# VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DYSLIPIDEMIA** IN PRIMARY CARE

Veterans Health Administration
Department of Defense

*Prepared by:*

# THE MANAGEMENT OF DYSLIPIDEMIA

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The Office of Performance and Quality, VHA, Washington, DC
External Peer Review Program

Contractor:
Birch & Davis Associates, Inc.

Contract number: DASW01-95-D-0026

December 2001
Version 1.2

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# VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DYSLIPIDEMIA** IN PRIMARY CARE

## INTRODUCTION

# MANAGEMENT OF DYSLIPIDEMIA IN PRIMARY CARE

## Introduction

Dyslipidemia is widely regarded as a major risk factor for coronary heart disease (CHD) and atherosclerotic cardiovascular disease (ASCVD) (NCEP II, 1993). It is thus a serious public health problem in the Department of Defense (DoD), the Veteran Health Administration (VHA) health care system, and in the nation at large. The Global Burden of Disease Study has estimated that cardiovascular disorders are currently the second leading worldwide cause of disability adjusted life years (the sum of lost life due to mortality and years of life adjusted for the severity of disability) in industrialized countries (Murray, 1997). Projections into the future suggest that cardiovascular disorders will rise to become the most important cause of disability adjusted life years. Based on the above statistics, there is little doubt that dyslipidemia is a major risk factor for morbidity and mortality within the DoD and VHA communities.

Lipid-related risk factors for ASCVD include high levels of total cholesterol or low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C) (NCEP II, 1993). Other risk factors include age, male sex, high blood pressure, tobacco use, diabetes mellitus, and family history of premature coronary heart disease (ACP, 1998). Because of the range of risk factors, targeted screening is recommended. All adults—regardless of age—who have a history of ASCVD should undergo lipoprotein screening, but for asymtomatic individuals (i.e. for primary prevention) available evidence supports cholesterol screening only if other characteristics place them at high risk. The debate over screening recommendations thus centers on young people without risk factors and older people without a history of ASCVD (ACP, 1998).

Evidence that lipid-related interventions reduce the ASCVD risk of patients with high cholesterol is well established for those with preexisting atherosclerotic disease (Canner et al., 1986; Scandanavian Simvastatin Survival Study Group (4S), 1994; Sacks et al., 1996), but the benefit of therapy is much less for those without disease (Downs et al., 1998). The current National Cholesterol Education Program (NCEP II) recommendations put increased emphasis on physical activity and weight loss as components of the nonpharmacologic therapy of dyslipidemia (NCEP II, 1993). If nonpharmacologic treatment is not successful there are several drug treatment options, most of which can be adequately managed in the primary care setting (NCEP II, 1993).

## Guideline Development Process

In 1994, a guideline for the Treatment of Cardiovascular Disease was developed for the VHA. The initial guideline was the product of a research and consensus building effort among professionals from throughout the VHA: cardiologists, social workers, nurses, administrators, primary care physicians, external peer review physicians and expert consultants in the field of guideline and algorithm development. This updated guideline for the Management of Dyslipidemia in Primary Care was started in mid-1999, at a meeting that also launched the development of a companion guideline, the Management of Ischemic Heart

Disease (IHD) in Primary Care. During the past two years, the DoD has participated with the VHA on guideline development and dissemination. This guideline is the product of this close collaboration.

The current guideline for the management of dyslipidemia represents hundreds of hours of diligent effort on the part of participants from the DoD, VHA, academia, and a team of private guideline facilitators. An experienced moderator facilitated the multidisciplinary panel that included internists, family practitioners, cardiologists, nurses, pharmacists, medical nutrition therapists, and rehabilitation specialists. Policy-makers and civilian practitioners joined these experts from the DoD and VHA. The process is evidence-based whenever possible. Where evidence is ambiguous or conflicting, or where scientific data are lacking, the clinical experience within the room was used to guide the development of consensus-based recommendations.

The goal in developing this guideline was to incorporate information from several existing, national recommendations into a format which would maximally facilitate clinical decision-making (Woolf, 1992). This effort drew heavily from the following sources:

- Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on the detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). (2001). Journal of the American Medical Association. 285(19), 2486-2497.

- NIH Consensus Conference on triglyceride, high-density lipoprotein, and coronary heart disease. JAMA 1993;269(4):505-10

- American College of Physicians (ACP) Guidelines for using serum cholesterol, high-density lipoprotein cholesterol, and triglyceride levels as screening tests for preventing coronary heart disease in adults. Ann Int Med 1996;124:515-17

- The U.S. Preventive Services Task Force Guide to Clinical Preventive Services. Second Edition 1996:15-38

- Pharmacy Benefits Management—Medical Advisory Panel. The pharmacologic management of hyperlipidemia. VHA PBM-SHG Publication. Hines, IL: Pharmacy Benefits Management Strategic Health Group, Veterans Health Administration, Department of Veterans Affairs, 1999.

We are confident that the current guideline represents a significant step forward for primary health care in the DoD and VHA. However, it is only the first step in the mission to improve the care of those with dyslipidemia. In the future, the challenge will be in:

- Guideline implementation
- Guideline promotion
- Development of teaching tools for graduate and continuing medical education

- Development of automation tools that include:
  - Provider specific report cards
  - Performance monitors that assist the practitioner/facility in outcome tracking based on guideline use.

The guideline/algorithms are designed to be adapted to an individual facility's needs and resources. They will also be updated periodically or when relevant research results become available. The guideline should be used as a starting point for innovative plans that improve collaborative efforts and focus on key aspects of care. The system-wide goal is to improve local management of patients with dyslipidemia and thereby improve patient outcomes.

The clinical practice guideline is presented in an algorithmic format. There are indications that this format improves data collection and clinical decision-making and helps to change patterns of resource use. A clinical algorithm is a set of rules for solving a clinical problem in a finite number of steps. It allows the practitioner to follow a linear approach to the recognition and treatment of dyslipidemia. It is recognized, however, that clinical practice often requires a nonlinear approach, and must always reflect the unique clinical issues in an individual patient-provider situation. The use of guidelines must always be considered as a recommendation within the context of a provider's clinical judgment in the care for an individual patient.

A clinical algorithm diagrams a guideline into a step-by-step decision tree. The steps in this tree are represented as a sequence of actions (rectangle "do boxes") and questions (hexagonal "decision boxes"). A letter within a box of an algorithm refers the reader to the corresponding annotation. The annotations elaborate on the recommendations and statements that are found within each box of the algorithm. These annotations include a reference, when required, and evidence grading for each recommendation. The strength of the recommendation (SR) and the quality of the evidence (QE) are both noted. The reference list at the end of each annotation includes all the sources used—directly or indirectly—in the development of the annotation text. A complete bibliography is provided at the end of the document.

## Literature

The literature supporting the decision points and directives in this guideline is referenced throughout the document. The working group leaders were solicited for input on focal issues prior to a review of the literature.

A search was carried out using the National Library of Medicine's (NLM) MEDLINE database. The term "hyperlipidemia" was searched along with the following Boolean expressions AND terms:

- Epidemiology
- Screening
- Diagnosis
- Primary Care
- Protocols
- Therapy
- Patient Education
- Economics.

Qualifiers dealing with specific types of publications (e.g. meta-analysis) were also used. Furthermore, two discreet delimiters framed each query:

- Articles published between 1994 and 1999, with some exceptions
- English language only.

Sixty-two articles were identified for inclusion in a table of information that was provided to each expert participant. The table of information contained:

- Title
- Author(s)
- Author(s) affiliation
- Publication type
- Abstract
- Source
- Relevance.

Copies of these tables were made available to all participants. Copies of specific articles were provided on an as needed basis.

The working group reviewed the articles for relevance and graded the evidence using the following rating scheme, published by the U.S. Preventive Services Task Force (U.S. PSTF, 1996).
The U.S. Preventive Services rating scheme:

**Strength of Recommendation (SR)**

| | |
|---|---|
| A | There is good evidence to support the recommendation that the condition be specifically considered. |
| B | There is fair evidence to support the recommendation that the condition be specifically considered. |
| C | There is insufficient evidence to recommend for or against the inclusion of the condition, but recommendations may be made on other grounds. |
| D | There is fair evidence to support the recommendation that the condition be excluded from consideration. |
| E | There is good evidence to support the recommendation that the condition be excluded from consideration. |

**Quality of Evidence (QE)**

| | |
|---|---|
| I | Evidence obtained from at least one properly randomized controlled trial. |
| II-1 | Evidence obtained from well-designed controlled trials without randomization. |
| II-2 | Evidence obtained from well-designed cohort or case-control analytical studies, preferably from more than one center or research group. |
| II-3 | Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence. |
| III | Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees. |

The QE rating is based on the quality, consistency, reproducibility, and relevance of the studies. Information about harmful effects must also be presented. The SR rating is influenced primarily by the science. Other factors that are taken into consideration when making a SR determination are:

- The burden of suffering
- Cost issues
- Policy concerns.

For many recommendations, there is insufficient evidence to determine whether or not routine intervention will improve clinical outcomes. Lack of evidence of effectiveness does not mean there is evidence of ineffectiveness. Rather, lack of evidence (SR = C) means:

- Insufficient statistical power or
- Unrepresentative populations or
- Lack of clinically important endpoints or

- Design flaws (USPSTF, 1996).

The experts themselves, after an orientation and tutorial on the evidence grading process, formulated QE and SR ratings. Each reference was appraised for scientific merit, clinical relevance, and applicability to the populations served by the Federal health care system. Recommendations were based on consensus of expert opinions and clinical experience only when scientific evidence was unavailable.

The assembled experts were an invaluable source of additional information and suggested numerous references. These were distributed to participants on an as needed basis. It must be noted that this document does not, however, include reference to any publications dated after December, 1999. More recent information will be included in future guideline updates.

**Performance Measurement**

The inability of consumers and health care purchasers to determine if medical care is appropriate and effective has given rise to the concept that the health care system should be held accountable for what is done and the outcomes achieved. This principle of accountability has resulted in the development of so-called "performance and outcome measures," administered through "report card" systems. Measures must be seen as fair and reasonable, and able to be carried out in various practice settings.

Performance measures are indicators or tools to assess the level of care provided to populations of patients. The measures are constructed to make the best use of the evidence available for assessing care or outcomes in systems where patient characteristics (e.g. co-morbidity) and compliance cannot be easily determined and taken into consideration (i.e. the measures are not case-mix adjusted).

The VHA instituted performance measures for implementation of clinical practice guidelines in FY 1998. These measures included screening for lipid abnormalities in diabetic patients and patients with established CHD. Along with the work on the current guideline itself, both VHA and DoD are developing additional performance measures.

## Overview of the Dyslipidemia Guideline

The Management of Dyslipidemia guideline is a single module that addresses three aspects of lipid-related care:

Algorithm, page 1 Dyslipidemia Screening

Algorithm, page 2-3 Management of Dyslipidemia in Primary Care: Primary Prevention

Algorithm, page 4 Management of Dyslipidemia in Primary Care: Secondary Prevention

This guideline also contains appendices that provide more information on the spectrum of treatment options, and give details on pharmacologic and other interventions.

Appendix 1. Medical Nutrition Therapy

# MANAGEMENT OF DYSLIPIDEMIA IN THE PRIMARY CARE SETTING

## Bibliography for Introduction

American College of Physicians: Guidelines for using serum cholesterol, high-density lipoprotein cholesterol, and triglyceride levels as screening tests for preventing coronary heart disease in adults (part 1). (1996). Annals of Internal Medicine, 124, 515-517.

Canner, P. L., Berge, K. G., Wenger, N. K., Stamler, J., Friedman, L., Prineas, R. J., & Friedewald, W. (1986). Fifteen year mortality in coronary drug project patients: long term benefit with niacin. Journal of the American College of Cardiology. 8(6),1245-1255.

Downs, J. R., Clearfield, M., Weis, S., Whitney, E., Shapiro, D. R., Beere, P. A., Lagendorfer, A., Stein, E. A., Kruyer, W., & Gotto, A. M. Jr. (1998). Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Journal of the American Medical Association, 279(20), 1615-1622.

Murray, C. J. L., Lopez, A. D. (1997). Global mortality, disability, and the contribution of risk factors: Global Burden of Diseases Study. Lancet, 349(9063), 1436-1442.

Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on the detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). (2001). Journal of the American Medical Association. 285(19), 2486-2497.

NIH Consensus Conference on triglyceride, high-density lipoprotein, and coronary heart disease. (1993). Journal of the American Medical Association, 269(4), 505-510.

Pharmacy Benefits Management—Medical Advisory Panel. (1999).The pharmacologic management of hyperlipidemia. VHA PBM-SHG Publication. Hines, IL: Pharmacy Benefits Management Strategic Health Group, Veterans Health Administration, Department of Veterans Affairs.

Sacks, F. M., Pfeffer, M. A., Moye, L. A., Rouleau, J. L., Rutherford, J. D., Cole, T. G., Brown, L., Warnica, F. W., Arnold, J. M., Davis, B. R., & Braunwald, E. (1996). Cholesterol and Recurrent Events Trial Investigators (CARE). The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. New England Journal of Medicine. 335(14), 1001-1009.

Scandinavian Simvastatin Survival Study Group: Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). (1994). Lancet, 344, 1383-89.

Society for Medical Decision Making Committee on Standardization of Clinical Algorithms. (1992). "Proposal for clinical algorithm standards," In Medical Decision Making, 12(2), 149-154.

The U.S. Preventive Services Task Force Guide to Clinical Preventive Services. Second Edition (1996). 15-38.

VA 1996 External Peer Review Program, Contract No. V101(93) P-1369.

VHA Directive 96-053, (August 29, 1996). Roles and Definitions for Clinical Practice Guidelines and Clinical Pathways.

Woolf, S. H. (May 1992) Practice guidelines, a new reality in medicine II. Methods of developing guidelines. Archives of Internal Medicine, 152. 947-948.

Woolf, S. H. (Dec 1993). Practice guidelines, a new reality in medicine III. Impact on patient care. Archives of Internal Medicine, 153, 2647.

# VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DYSLIPIDEMIA** IN PRIMARY CARE

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# VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DYSLIPIDEMIA** IN PRIMARY CARE

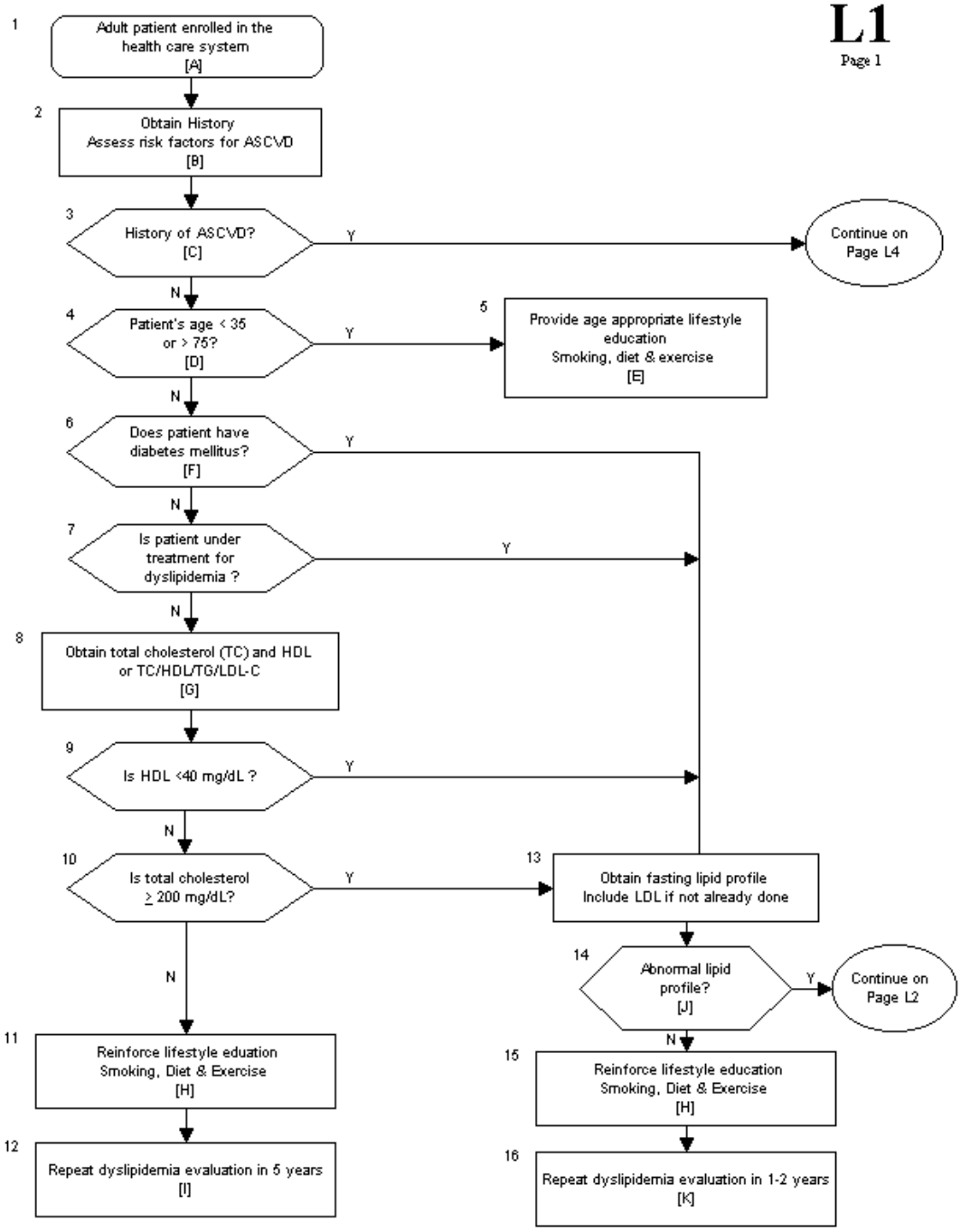
## ALGORITHMS AND ANNOTATIONS

# VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DYSLIPIDEMIA** IN PRIMARY CARE

## ALGORITHMS

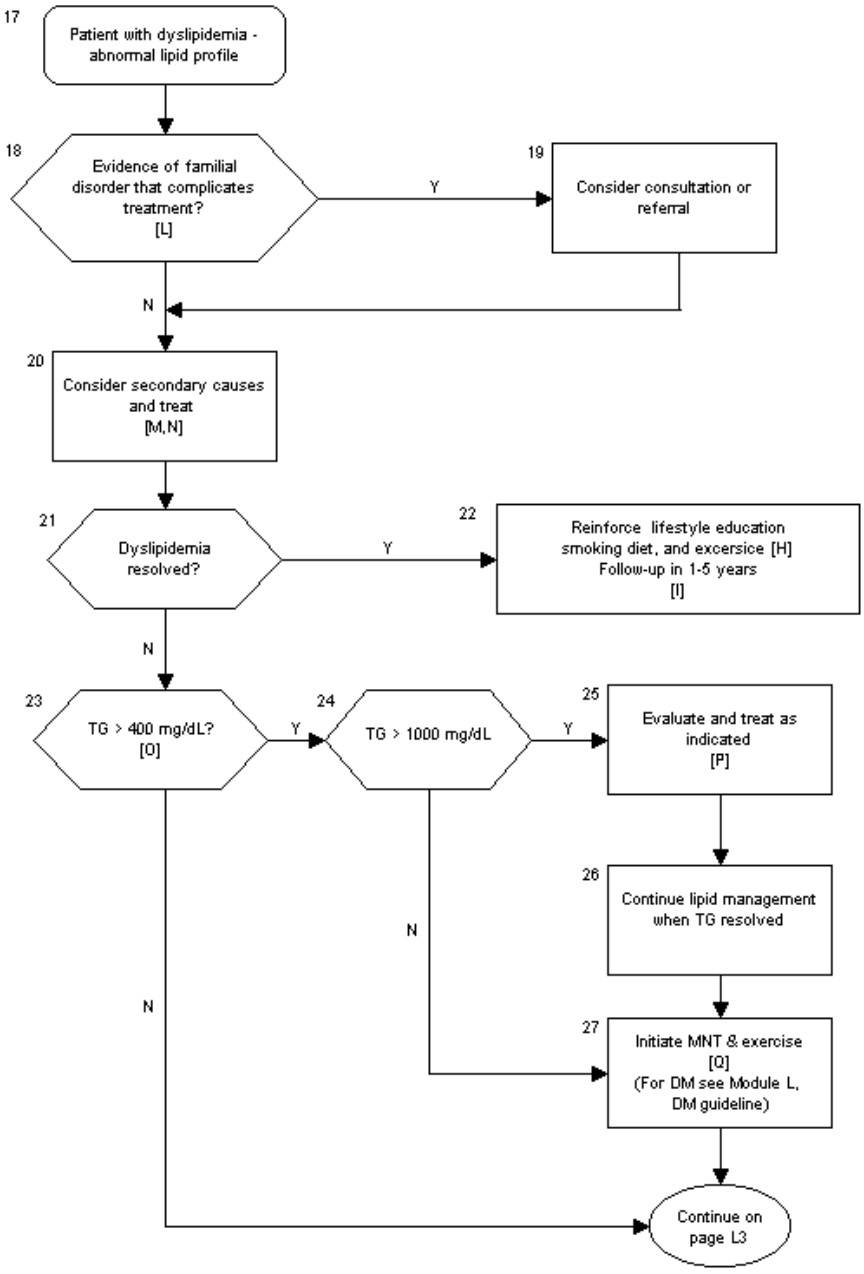
## Management of Dyslipidemia in Primary Care Screening

**L1**
Page 1



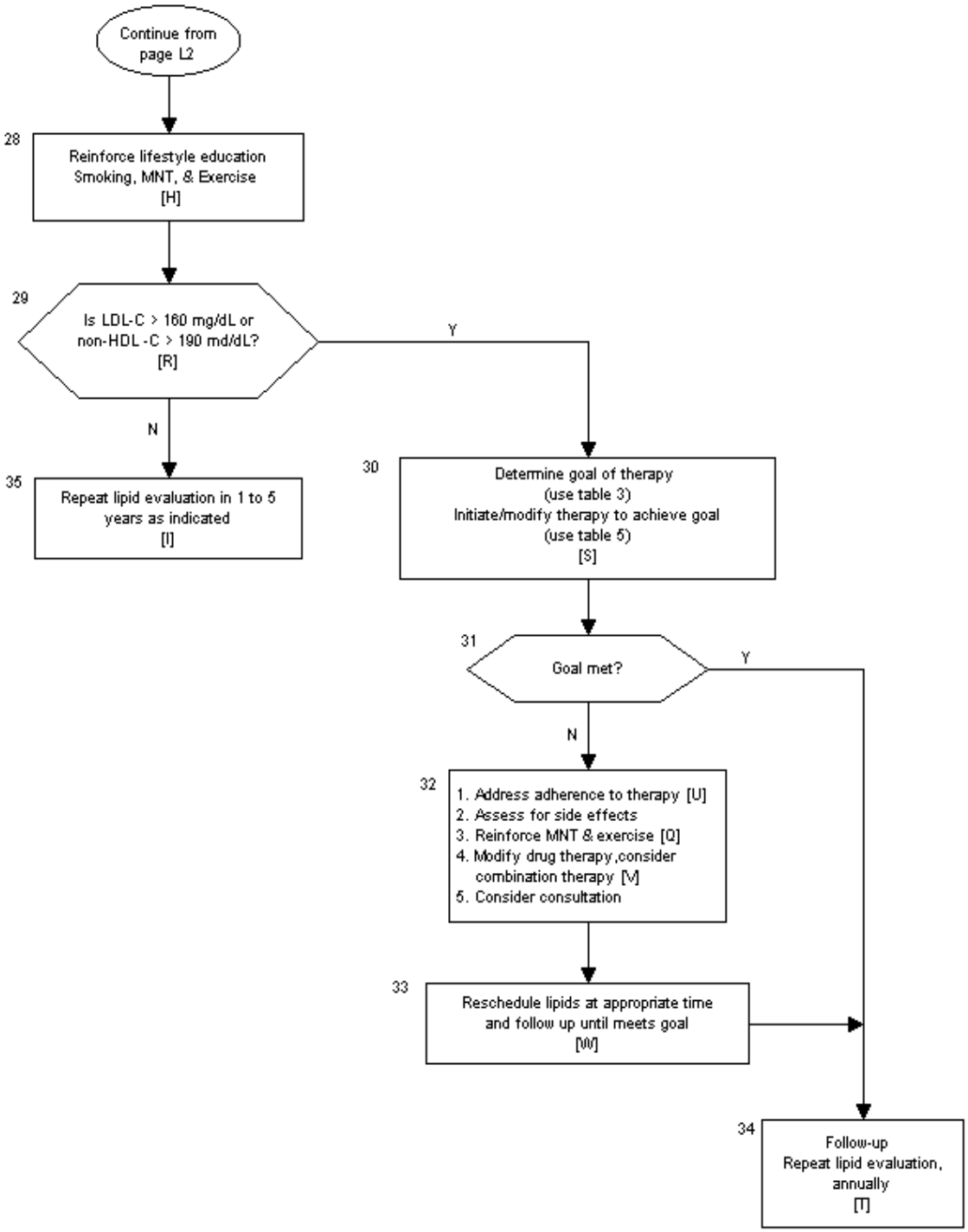
**Management of Dyslipidemia in Primary Care**
**Primary Prevention**

**L2**
Page 2



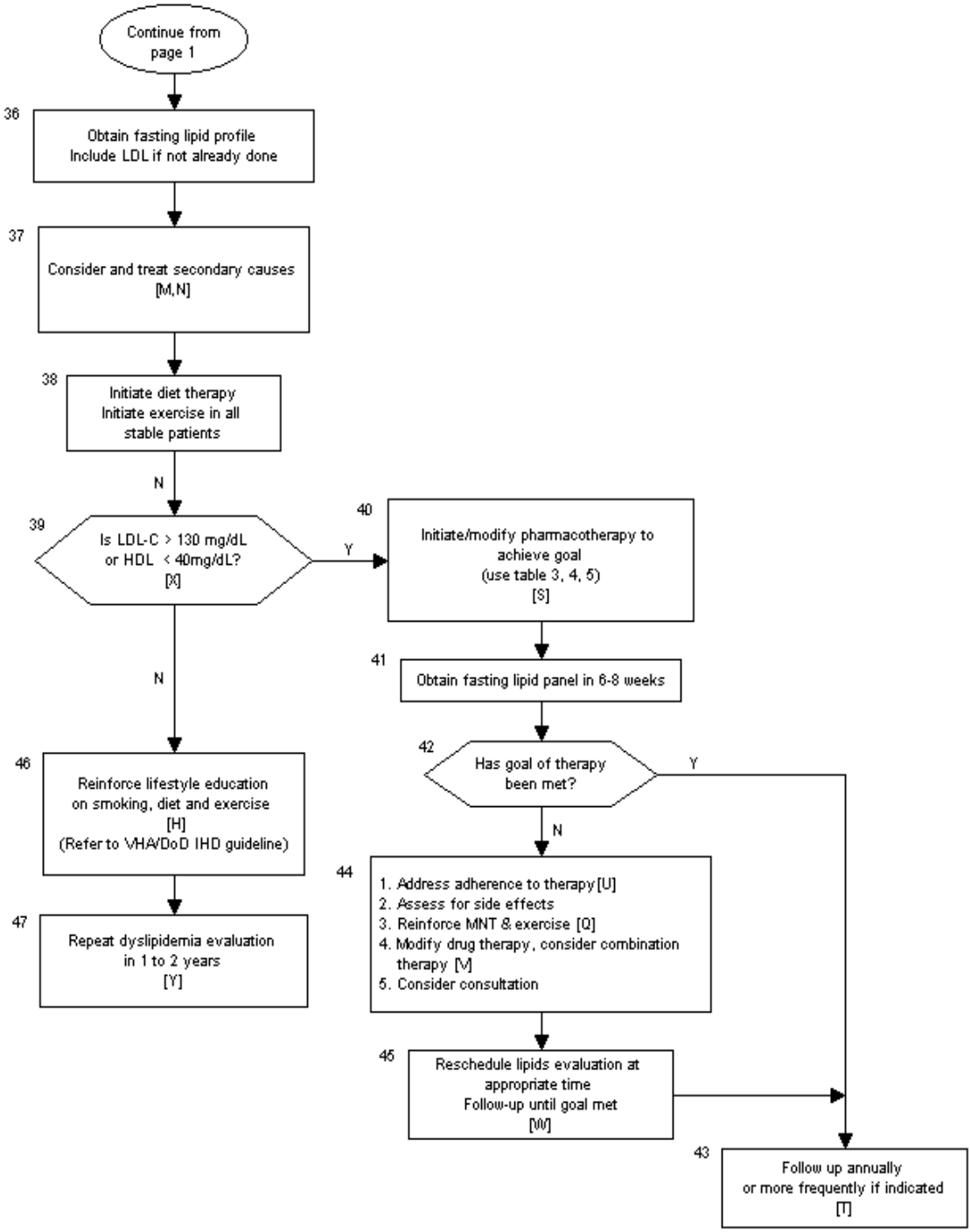
## Management of Dyslipidemia in Primary Care
## Primary Prevention

**L3**
Page 3



## Management of Dyslipidemia in Primary Care
## Secondary Prevention

**L4**
Page 4



# VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DYSLIPIDEMIA** IN PRIMARY CARE

## ANNOTATIONS

# Management of Dyslipidemia in Primary Care

## A. Adult Patient Enrolled in the Health Care System

DEFINITION

Any adult (> age 17) who is eligible for care in the Department of Defense (DoD) or Veterans Health Administration (VHA) health care delivery system should be screened for dyslipidemia as described in this guideline.

## B. Obtain History. Assess Risk Factors for Atherosclerotic Cardiovascular Disease (ASCVD)

OBJECTIVE

To identify clinical markers that predict an increased risk for developing ASCVD, thereby changing the interpretation of LDL levels.

ANNOTATION

A high low-density lipoprotein (LDL) cholesterol level is a strong predictor of cardiovascular (CV) risk, although in the absence of other CV risk factors the absolute risk for developing ASCVD is still relatively low. Conversely, the presence of other recognized CHD risk factors magnify the risk associated with any level of LDL. Proven, independent, clinical predictors of increased risk for ASCVD (in addition to elevated LDL cholesterol) include:

1. Age (males > 45 years, females > 55 years or menopause < age 40?)
2. Family history of premature coronary artery disease; definite myocardial infarction (MI) or sudden death before age 55 in father or other male first-degree relative, or before age 65 in mother or other female first-degree relative
3. Current cigarette smoker
4. Hypertension (systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg confirmed on more than one occasion, or current therapy with antihypertensive medications)
5. Diabetes mellitus (DM)
6. High-density lipoprotein (HDL)-cholesterol < 40 mg/dL

"Negative" Risk Factor

Elevated HDL cholesterol, > 60 mg/dL, is a well-established independent, clinical predictor of decreased risk for ASCVD. It has been suggested that an HDL > 60 mg/dL negates one ASCVD risk factor for individual risk calculation.

DISCUSSION

Several large trials, including the Framingham Heart Study (Castelli, 1984) and the Multiple Risk Factor Intervention Trial Research Group (MRFIT, 1982; Neaton & Wentworth, 1992), have identified non-LDL cholesterol risk factors that predict a person's risk for developing ASCVD. Importantly, these risk factors are more than additive to one another. The single most important risk factor for having a myocardial infarction is established cardiovascular disease. Approximately 50 percent of all myocardial infarctions occur in people with known cardiovascular disease. Further discussion of non-cholesterol risk factors for IHD is in the VHA/DoD Guideline for Ischemic Heart Disease (IHD).

Multiple epidemiologic studies including the Framingham Study have observed an inverse relation between HDL levels and risk for coronary heart disease, where a difference of one mg/dL is associated with a 2-3 percent change in risk (Gordon et al., 1989). In the Framingham Study, for instance, men with an HDL lower than 25 mg/dL had an incidence of coronary heart disease of 176.5/1000, whereas men with an HDL of 25 to 34 mg/dL had an incidence of coronary heart disease of 100.0/1000. Likewise, women with an HDL of 25 to 34 mg/dL had an incidence of coronary heart disease of 164.2/1000, whereas women with an HDL of 35 to 44 mg/dL had an incidence of 54.5/1000. The importance of low HDL as a risk factor for developing coronary heart disease was borne out in the AFCAPS/TexCAPS trial, in which the most significant benefit was seen in patients treated with an entry HDL lower than 35 mg/dL (Downs et al., 1998). Just as a low HDL level is inversely linked to an increased risk for developing coronary heart disease, so a high HDL level is inversely linked to a decreased risk for developing coronary heart disease (Wilson et al., 1988). It has been established that the protective effect of a high HDL is present even in the setting of a high LDL (Kannel, 1978).

EVIDENCE

*LDL*. (QE=I, SR=A). MRFIT, 1982; Neaton & Wentworth, 1992; Castelli, 1984

*HDL*. (QE=II-2, SR=A). Gordon et al., 1989; Downs et al., 1998; Wilson et al., 1988; Kannel, 1978

**C. Does Patient Have a History of ASCVD?**

OBJECTIVE

Prompt identification of patients known to benefit from lipid lowering therapy.

ANNOTATION

All patients with known CHD (history of myocardial infarction [MI], angina pectoris, other evidence of CHD) or a history of other kinds of vascular disease (such as stroke or claudication) are at high risk for coronary ~~cardiac~~ events. Prevention of recurrent and fatal coronary events via aggressive lipid-lowering therapy has been demonstrated in large clinical trials.

## DISCUSSION

Secondary prevention refers to patients with known CHD or ASCVD. Trials with a variety of hypolipidemic drugs have shown that therapy of dyslipidemias not only improves LDL and/or HDL profiles, but also reduces fatal and non-fatal coronary events (4S, 1994; CARE, 1996; LIPID, 1998; VA-HIT, 1999), angiographic progression (CLAS, 1987; FATS, 1990), and CHD mortality and total mortality (Oslo, 1986; Oslo, 1995; 4S, 1994; LIPID, 1998; FLARE, 1999).

There are no large randomized controlled trials (RCTs) on lipid therapy in secondary prevention for peripheral vascular disease. Meta-analysis and subgroup analysis from CHD trials has shown that statin or niacin therapy reduces the incidence of stroke. A Cochrane review found that cholesterol-lowering therapy reduces progression of peripheral vascular disease (Leng et al., 1999).

## REFERENCES

Scandanavian Simvastatin Survival Study Group (4S), 1994; Sacks (CARE), 1996; Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group, 1998; VA-HIT, 1999; Blandenhorn et al. (CLAS), 1987; Brown et al. (FATS), 1990; Hjermann et al. (Oslo), 1986; Anderssen et al. (Oslo), 1995; Surruys et al. (FLARE), 1999; Post CABG Trial, 1997, Leng et al., 1999, NCEP III, 2001.

**D. Is Patient Younger than 35 Years or Older than 75 Years?**

OBJECTIVE

To screen the segment of the beneficiary population most represented in randomized controlled trials of hyperlipidemia intervention.

ANNOTATION

At a population level, patients of any age may benefit from general lifestyle recommendations to curtail dietary saturated fat and to perform aerobic exercise several times per week, regardless of the results of lipid screening. Targeted lipid screening of males aged 35 to 75 years and females aged 45 to 75 years is recommended in the primary prevention setting, based on the results of RCTs of lipid interventions. For every given age, the ASCVD risk for a female is the same as that for a male 10 years her junior.

The recommendation for screening up to age 65 is based on strong clinical and epidemiologic evidence. The recent AFCAPS/TexCAPS trial results (Downs et al., 1998) suggest that treating patients age 65-73 is beneficial. Epidemiologic evidence suggests benefit in ages 65 to 75. The association of cholesterol and mortality weakens in elderly patients, and screening is not recommended for primary prevention after age 75.

The risk of ASCVD is so low in males younger than 35 years and females younger than 45 years that screening cannot be recommended unless there is an unusual family history of coronary events occurring prior to age 45.

REFERENCES

American College of Physicians (ACP), 1996; USPSTF, 1996; NCEP III, 2001; Downs et al., 1998

**E. Provide Age-Appropriate Lifestyle Education on Smoking, Diet, and Exercise**

OBJECTIVE

To promote lifestyle changes that will decrease the risk of ASCVD.

ANNOTATION

Smoking, diet, and activity level are important modifiable predictors of risk for ASCVD (McGinnis and Foege, 1993). Primary care clinicians can have a positive effect on health behaviors and should provide and/or arrange for age-appropriate lifestyle education. The top three lifestyle behaviors associated with premature death are:

| *Risk* | *Recommended Intervention* |
|---|---|
| • Smoking | Advise smokers/tobacco users to quit. |

- Diet — Provide basic information about managing a healthy diet (using the U.S. Department of Agriculture Dietary Guidelines for Americans, 1992).
- Sedentary lifestyle — Encourage 30 minutes or more of moderate intensity activity on most days of the week.

Many experts also recommend attention to the following additional lifestyle modifications:

- Limitation of alcohol intake to one or two drinks per day
- Reduced calorie diet to promote weight loss, if overweight
- Stress management.

DISCUSSION

Smoking, diet and exercise habits are prominent modifiable risk factors to be considered in preventive efforts (McGinnis and Foege, 1993). Clinical trials, as well as epidemiologic studies, support the association of a high-fat/cholesterol diet, sedentary lifestyle and obesity with risk of ASCVD (Califf et al., 1996; Berlin and Colditz, 1990; Beresford et al., 1997; McCarron et al., 1997). All patients need to be advised on lifestyle changes as a matter of general health (NCEP III, 2001), and appropriate referral for counseling may be advisable.

There is evidence that ASCVD risk is improved with the following:

**Smoking Cessation**

Smoking cessation is one of the most effective ways to reduce risk for ASCVD and other atherosclerotic diseases (USDHHS, 1989; Rosenberg et al., 1985; Rosenberg et al., 1990). Smokers are motivated toward smoking cessation by a physicians' advice to quit (NCI, 1994; Ockene, 1987; Ockene et al., 1991; Pederson, 1982). Research demonstrates that the physician's advice to quit smoking increases quit rates compared with the absence of such advice (USDHHS, 1989). Furthermore, there is substantial evidence that even brief smoking cessation treatments can be effective (Fiore et al., 1994; Glynn & Manley, 1990). All physicians should strongly advise every patient who smokes to quit. (See also VHA/DoD guidelines for Tobacco Use Cessation)

**Regular Aerobic Activity**

A sedentary lifestyle is associated with a twofold increase in ASCVD risk (Blair, 1994). Clinicians should advise patients of all ages to follow a well-balanced exercise plan consisting of stretching, aerobic activity, and strengthening (Mazzeo et al., 1998). Although the exact exercise parameters for optimal ASCVD prevention have been difficult to determine, research clearly demonstrates a dose-response relationship to risk reduction with

increasing activity and caloric expenditure (Pate et al., 1995; Joint British recommendations, 1998). Therefore, current exercise guidelines for the general population recommend that every adult in the United States accumulate 30 minutes or more of moderate intensity physical activity on most (and preferably all) days of the week (Pate et al., 1995; ACSM, 1995; Pollock & Wilmore, 1990; Spate-Douglas et al., 1999). Consider referring patients who need specialized exercise programs to an exercise professional.

**A "Prudent" Low-fat, Low-cholesterol Diet**

Providers should reinforce the importance of the Dietary Guidelines for Americans (USDA, 1992), with emphasis on limiting intake of saturated fat and cholesterol, moderating intake of sodium and alcohol, and increasing consumption of fruits, vegetables, and whole grains. Weight loss should be encouraged for the overweight.

It is recognized that changing behavior is difficult. Change may not occur despite the best of intentions and efforts. For example, the success rates of smoking cessation programs are low (15 to 20 percent); similar data apply to the achievement of significant weight reduction. Even when the behavior is changeable, the effort and resources required to bring about a clinically significant change may be better used in other efforts (Ebrahim & Davey Smith, 1999). Clinical judgment is needed to decide how much effort is reasonable and when to move on.

Despite these data, some patients do succeed, and there is as yet no way to identify them. Thus, reasonable efforts to change behaviors need to be made when indicated, and both the efforts and the results documented.

There is evidence that a physician's communication skills can positively influence not only patient satisfaction but also patient compliance with specific recommendations (Hall et al., 1988; Ockene et al, 1991). Since physicians may have insufficient time with patients to adequately address behavior change, referrals may be helpful. The Department of Defense and the VA have resources in place to provide educational services, such as wellness centers, nutritional counselors, and formal smoking cessation programs.

EVIDENCE

*Smoking*. (QE=I, SR=A). USDHHS, 1989; NCI, 1994; Ockene, 1987; Ockene et al., 1991; Fiore, 1994

*Diet*. (QE=I, SR=A). USPSTF, 1996; Beresford et al., 1997; McCarron et al., 1997

*Exercise*. (QE=I, SR=A). Pate et al., 1995; ACSM, 1995; Pollock & Wilmore, 1990; Spate-Douglas et al., 1999

*Lifestyle changes promote general health*. (QE=III, SR=A). NCEP III, 2001.

*Changing behavior is very difficult*. (QE=I, SR=A). Ebrahim & Davey Smith, 1999

**F. Does Patient Have Diabetes Mellitus?**

OBJECTIVE

To promote the prompt identification and aggressive management of lipid disorders identified in patients known to be diabetic.

ANNOTATION

- Patients with DM are at significantly increased risk of CHD compared with non-diabetic patients of similar age.
- DM patients without known CHD appear to have a risk for first MI similar to the risk for recurrent MI of non-DM patients with CHD and a prior coronary event.
- Patients with type 2 diabetes commonly have other risk factors (hypertension, high LDL-C, low HDL-C, obesity) that increase risk for cardiac events.

DISCUSSION

Type 2 DM is associated with a two-fold to four-fold increase in ASCVD. The MRFIT study (1982; Neaton & Wentworth, 1992) confirmed that DM is an independent risk factor for CHD. The morbidity and mortality from coronary events in diabetic patients are substantial, and exceed those in non-DM patients. In particular, patients with type 2 DM appear to have disproportionate risk for CHD morbidity and mortality. Haffner et al. (1998) found in a Finnish population-based study that patients with diabetes had an incidence of first MI (20.2%) similar to the incidence of recurrent MI among non-DM patients with known prior MI (18.8%) over a seven-year period of observation. In this study, the hazard ratio for death from coronary heart disease for diabetic subjects without prior myocardial infarction as compared with nondiabetic subjects with prior myocardial infarction was not significantly different from 1.0 (hazard ratio, 1.4). Of note, mean LDL of both diabetic and non-diabetic patients observed in this study was over 180 mg/dL; HDL was 10 mg/dL lower in diabetic as compared with non-diabetic patients; and two-thirds of the diabetic subjects were hypertensive, versus one-third of the non-diabetic subjects.

The exact explanation for the increased morbidity and mortality is unknown, but cannot be primarily attributable to glycemic control Although the UKPDS (1998) found fewer CHD/ASCVD events in the "intensive" glycemic control group compared with the "control" group the difference only approached—but did not reach—statistical significance. There were too few CHD/ASCVD events in both the "intensive" glycemic control and "usual" glycemic control groups in the DCCT (1993) to ascertain whether or not glycemic control conferred a risk reduction benefit. Ongoing studies, including the NHLBI ACCORD Trial and the VA Cooperative Study 465 are investigating whether intensive glycemic control will improve macrovascular outcomes in type 2 diabetes.

Since elevated LDL cholesterol is known to be associated with an increased risk for CHD, management of hyperlipidemia has become a focal point in the management of the diabetic

patient. Treatment options for the diabetic patient exhibiting "diabetic dyslipidemia" (low HDL, elevated triglycerides, normal-to-slightly elevated LDL) include aggressive LDL lowering, as in secondary CHD prevention in non-diabetic patients, or triglyceride-lowering therapy with a fibrate drug (such as gemfibrozil), which usually also raises HDL. A secondary CHD prevention trial, the VA-HIT study (1999), randomized patients to gemfibrozil or usual care for low HDL cholesterol, and demonstrated comparably reduced CHD event rates in both diabetic and non-diabetic patients. Based on the observation of the Haffner study (1998) that patients with type 2 DM have the same risk of first MI as do non-DM patients for recurrent MI, many health care providers may choose to offer gemfibrozil treatment to diabetic patients who have low HDL, hypertriglyceridemia, and normal LDL as part of a primary CHD prevention strategy.

Presently, the NCEP ATPIII and American Diabetes Association (ADA) guidelines (2001) for lipid management in diabetic patients designate LDL > 130 mg/dL as "high risk," and recommend initiation of aggressive dietary and/or drug therapy at this degree of hypercholesterolemia. Although LDL-C levels of <100 mg/dl are noted as "optimal", both organizations recognize the evolving evidence in the 100-129 mg/dl LDL-C range through the following statement:

*"If LDL cholesterol levels are 100-129 mg/dL, either at baseline or on LDL-lowering therapy, several therapeutic approaches are available:*

- *Initiate or intensify lifestyle and/or drug therapies specifically to lower LDL.*
- *Emphasize weight reduction and increased physical activity in persons with the metabolic syndrome.*
- *Delay use or intensification of LDL-lowering therapies and institute treatment of other lipid or nonlipid risk factors; consider use of other lipid-modifying drugs (eg, nicotinic acid or fibric acid) if the patient has elevated triglyceride or low HDL cholesterol*." (NCEP III, 2001)

Respecting the relative absence of evidence in regard to efficacy of hypolipidemic drug therapy for LDL-C in the 100-129 mg/dl range, the VA/DOD Guideline development group recommends aggressive MNT for all such patients.

EVIDENCE

*Diabetes is an independent risk factor*. (QE=II-2, SR=B). MRFIT, 1982; Neaton & Wentworth, 1992, Stamler et al., 1993; Haffner, 1998

*Management of "diabetic dyslipidemia."* (QE=I, SR=A). VA-HIT, 1999; Rubins, et al., 1999

**G. Obtain Total Cholesterol (TC) and HDL *or* TC, HDL, TG, LDL**

OBJECTIVE

To risk-stratify patients for targeted intervention versus follow-up screening.

ANNOTATION

Lipid levels may be obtained in a fasting or nonfasting state. TC levels and HDL-C can be measured in the nonfasting patient. TG concentrations, however, are affected by recent food intake and will affect the calculation of LDL-C by the Friedewald equation: LDL-C = [TC] - [HDL-C] - [TG/5].

Nonfasting values differ from fasting values, but may still provide useful—though more limited—information. It may be inconvenient for the patient to return for a fasting sample. Costs may vary depending on which lipids (TC, HDL, LDL, VLDL, TG) are requested. At many institutions, a panel is available.

Clinical decisions should be based on two lipid profiles, done 1 to 8 weeks apart, which have an LDL-C or TC difference of < 30 mg/dL.

Recent myocardial infarction, stroke, surgery, trauma, or infection may transiently lower cholesterol levels up to 40 percent. If a lipid profile cannot be obtained immediately (within 12 to 24 hours of the event), one must wait 8 weeks post-event to obtain an accurate reading. Cholesterol levels increase by as much as 20 to 35 percent during pregnancy and should not be measured until three to four months after delivery.

DISCUSSION

The U.S. Preventive Services Task Force (USPSTF) recommends "using specimens obtained from fasting or nonfasting individuals" to screen for high cholesterol but that "there is insufficient evidence to recommend for or against measurement of HDL-C or triglycerides at initial screening" (USPSTF, 1996).

The TC/HDL ratio in some studies is thought to be the best predictor for both outcome and treatment benefits (Criqui & Golomb, 1998). Both the published 1998 British and European guidelines rely upon this ratio (Joint British Recommendations, 1998; Wood et al., 1998). The Canadian interim guidelines recommend treatment based on either TC/HDL or LDL levels (Frolich et al., 1998).

Intraindividual cholesterol measurement may vary up to 14 percent from an individual's average value (Cooper et al., 1992). The standard deviation of the differences in measured cholesterol values increases as the average cholesterol level increases. Although more accuracy is obtained by measuring multiple cholesterol specimens, the second sample produces the most change. In addition, "for modest changes in underlying cholesterol levels of about 10 percent…it will be impossible to say which individuals have achieved this simply by remeasuring their cholesterol" (Thompson & Pocock, 1990).

TC levels and HDL-C can be measured in the nonfasting patient. TG concentrations, however, are affected by recent food intake and will affect the calculation of LDL-C by the Friedewald equation:
LDL-C = [TC] - [HDL-C] - [TG/5]. Therefore, patients should be fasting for at least 12 hours prior to lipid profile determinations.

If the TG concentration is > 400 mg/dL, a calculated LDL-C is most often inaccurate. In some circumstances, a direct LDL-C measurement may be appropriate. Non-HDL-C (i.e. VLDL + IDL + LDL-C) may be used as an additional criterion.

REFERENCES

USPSTF, 1996; Criqui & Golumb, 1998; Joint British Recommendations, 1998; Wood et al., 1998; Frolich et al., 1998; Cooper et al., 1992; Thompson & Pocock, 1990

**H. Reinforce Lifestyle Education, Smoking, Diet, and Exercise**

Refer to Annotation E.

**I. Repeat Dyslipidemia Evaluation in 1 to 5 Years**

OBJECTIVE

To provide appropriate clinical follow-up for patients at initially low risk for ASCVD.

ANNOTATION 

If the initial dyslipidemia screening reveals total cholesterol < 200 mg/dL or LDL cholesterol < 130 mg/dL AND HDL cholesterol > 35 mg/dl, the patient—in the absence of other risk factors—will be of average or below average risk for atherosclerotic events over a five-year period.

Because total and LDL cholesterol tend to increase with advancing age, patients at initially average risk for ASCVD events may over time become patients at above-average risk or may develop concurrent health conditions (nephrotic syndrome, hypothyroidism, diabetes mellitus) that can declare as dyslipidemia. Re-assessment of serum cholesterol and HDL five years after an initially favorable dyslipidemia screening permits timely identification and treatment of such individuals.

EVIDENCE

*Appropriate follow-up*. (QE=III, SR=A). NCEP III, 2001; Lovastatin Study Groups, 1993; Jones, 1991

**J. Is Lipid Profile Abnormal?**

OBJECTIVE

To identify a group of patients who require further evaluation and/or therapy for hyperlipidemia.

ANNOTATION

Patients with the following results of lipid measurements will require therapy for a lipid disorder:

- LDL > 130 mg/dL
- HDL < 40 mg/dL
- TG > 400 mg/dL

DISCUSSION

Patients without known cardiovascular disease who have an LDL lower than 130 mg/dL and an HDL greater than 40 mg/dL have a low incidence of cardiovascular events. Because of this low incidence, the absolute benefit of drug treatment for hyperlipidemia is low. These patients should be counseled regarding good lifestyle behaviors including good dietary and exercise habits. Moderately elevated triglycerides (< 400 mg/dL) are usually responsive to low fat diet, weight reduction, and increase in physical activity. See Annotation E for further discussion.

**K. Repeat Dyslipidemia Evaluation in 1 to 2 Years**

OBJECTIVE

To provide appropriate clinical follow-up.

ANNOTATION

If the initial dyslipidemia screening reveals total cholesterol > 200 mg/dL but fasting LDL cholesterol < 130 mg/dL AND HDL cholesterol > 40 mg/dL, the patient will be of average risk for lipid-related events over a one to two year period.

DISCUSSION

Because total and LDL cholesterol tend to increase with advancing age, patients at initially average risk for ASCVD events may over time become patients at above-average risk or may develop concurrent health conditions (nephrotic syndrome, hypothyroidism, diabetes mellitus) that can declare as dyslipidemia. Periodic reassessment of serum cholesterol and HDL permits timely identification and treatment of such individuals.

REFERENCE

NCEP III, 2001

**L. Evidence of Familial Disorder that Complicates Treatment?**

OBJECTIVE

To promote the prompt identification and aggressive lipid management that is indicated for this group.

ANNOTATION

Most severe forms of hypercholesterolemia are the result of genetic disorders. Familial hypercholesterolemia is characterized by severe elevations of LDL cholesterol (> 260 mg/dL), tendon xanthomas, and premature CHD. Familial combined hyperlipidemia is characterized by elevations of total cholesterol, triglycerides, or both, in different members of the same family, and is associated with premature CHD. Patients presenting with very severe hypercholesterolemia should undergo family screening to detect other candidates for therapy. Therefore, a consultation with a specialist is recommended to assist the primary care clinician in co-managing these patients.

REFERENCE

NCEP III, 2001

**M. Consider and Treat Secondary Causes of Elevated LDL-C**

OBJECTIVE

To detect and, if needed, to treat health disorders that present as an elevated LDL-C.
Note: If a patient has hypertriglyceridemia, see Annotation N.

ANNOTATION

Hypothyroidism, chronic renal failure, and the nephrotic syndrome are well known to cause elevated LDL-C. Recognition of these conditions will focus attention on a potentially treatable underlying disorder. Cost-effective screening of the patient presenting with hypercholesterolemia might therefore include measurement of serum thyroid-stimulating hormone (TSH), BUN/creatinine, and a dipstick urinalysis, to exclude these relatively common conditions.

DISCUSSION

Hypothyroidism raises serum LDL. A normal serum TSH level adequately rules out the common condition of primary hypothyroidism. TSH alone cannot exclude the rare condition of secondary hypothyroidism (hypothalamic or pituitary insufficiency). If there is any clinical suspicion of this condition, serum thyroxine ($T_4$) should be measured. Normal TSH and normal $T_4$ effectively rule out the possibility of secondary hypothyroidism.

Treatment of severe hypothyroidism (manifested by very high TSH and/or very low $T_4$) with oral L-thyroxine replacement often lowers elevated LDL to the normal range; treatment of mild, or subclinical, hypothyroidism has considerably less impact on the serum LDL. In either case, serum lipids should be assayed six to eight weeks after normalization of the serum TSH (or $T_4$, in the case of secondary hypothyroidism) to see if any additional treatment is needed (Stone, 1997; NCEP III, 2001).

Nephrotic syndrome is a secondary cause of dyslipidemia (Stone, 1997; NCEP III, 2001). Nephrotic syndrome is characterized by excessive urinary protein excretion, which may be detected by routine dipstick urine testing. If the dipstick test is positive on two occasions, then a quantitative 24-hour measurement of urine protein needs to be done. If the quantitative assay shows a value in the nephrotic range ($\geq$ 3 g/day), referral to a nephrologist for further evaluation and management is appropriate.

Nephrosis may or may not account for a raised LDL level but is a serious matter in itself that needs careful attention. Nephrosis is a powerful predictor of end-stage renal disease in Type 1 DM and is probably a predictor of eventual renal failure in some patients with Type 2 DM as well. Although nephrosis in a patient with Type 2 DM is most likely due to diabetic nephropathy, an assessment for other causes can best be done by a nephrologist. (See VA/DoD guideline for Diabetes Mellitus Modules L and R.)

**Table 1. Address Secondary Causes of Lipid Abnormalities[a]**

| Disorder/Patient Characteristic | Effect on Lipids | Laboratory Test for Diagnosis |
|---|---|---|
| Chronic renal failure/ Postrenal transplantation | ↑ TG, ↑ TC, ↓ HDL-C | $S_{Cr}$ |
| DM | ↑ TG, ↑ TC, ↓ HDL-C | Glucose, HbA1c |
| Ethanol use | ↑ TG, ↑ HDL-C | |
| HIV/AIDS[b] | ↑ TG, ↓ TC, ↓ HDL-C, ↓ LDL-C | |
| Hypothyroidism[c] | ↑ TG, ↑ TC, ↑ LDL-C | TSH, thyroid hormones |
| Inactivity | ↓ HDL-C | |
| Nephrotic syndrome | ↑ TC, ↑ LDL-C | Urinalysis, serum albumin |
| Obesity | ↑ TG, ↓ HDL-C | |
| Obstructive liver disease | ↑ TC | LFTs |
| Estrogen therapy | ↑ TG, ↓ LDL, ↑ HDL | |

[a]AIDS = acquired immune deficiency syndrome; DM = diabetes mellitus; HbA1c = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; LFTs = liver function tests; $S_{Cr}$ = serum creatinine; TC = total cholesterol; TG = triglycerides; TSH = thyroid-stimulating hormone.

[b] Effects more pronounced with the addition of protease inhibitors
[c]Primary and secondary.

EVIDENCE

Address secondary causes: Stone, 1997; NCEP III, 2001
QE=III, SR=A.

**N. Consider and Treat Secondary Causes of Hypertriglyceridemia**

OBJECTIVE

To identify and address the secondary causes of hypertriglyceridemia.
Note: If patient has elevated LDL, see Annotation M.

ANNOTATION

The most common secondary causes of hypertriglyceridemia are alcohol, diabetes, and hypothyroidism. Addressing these underlying conditions can improve or normalize triglyceride levels, and failure to address these can render therapy ineffective.

DISCUSSION

Hypertriglyceridemia can be caused by or exacerbated by an underlying medical disorder. When secondary disorders of hyperlipidemia are appropriately treated, triglyceride levels can greatly improve or, in some cases, even return to the normal range. Hypertriglyceridemia has been associated with obesity and alcohol use/abuse. The need to screen for underlying alcohol use, together with a critical review of dietary habits, cannot be overemphasized (Oberman et al., 1992). Diabetes mellitus (especially suboptimally controlled), hypothyroidisim, nephrotic syndrome, hypogonadism, and obstructive liver disease have all been documented as potential causes for hypertriglyceridemia (See Table 1, Annotation M).

Some medications can have an incidental negative impact on a patient's lipid profile. Progestins, estrogens, androgens, anabolic steroids, corticosteroids, cyclosporine, and retinoids may raise cholesterol and/or triglyceride levels. A thorough review of the patient's chart and previous lipid panels may support the possibility of a drug side effect as the etiology for the lipid abnormality, or a trial off the suspected agent may be required for confirmation. Of note, oral estrogens have been associated with significant hypertriglyceridemia, which resolved with the discontinuation of the oral preparation. Many of these patients appear to be able to tolerate estrogen patch therapy without recurrence of the triglyceride elevations. Progestins have been shown to decrease HDL, thereby counteracting the HDL-raising effects of estrogen therapy.

It also must be stressed that even though many of the above disorders have been associated with secondary hyperlipidemia, they may be only an exacerbating factor, and not the primary cause, for the specific lipid elevation. Therefore, when treating potential causes of secondary hyperlipidemia, the provider is obligated to perform follow-up lipid levels at a reasonable time, usually two to three months, after correction of any such underlying disorder. Even with successful treatment of a secondary cause of hyperlipidemia, intervention with appropriate pharmacologic agents to lower cholesterol and/or trigylceride levels may be required.

The above discussion should only be considered as a short summary of the most common secondary causes of hyperlipidemia and should not be considered a complete list. Readers requiring further information are referred to current medical literature available on the subject.

REFERENCE

Oberman et al., 1992

**O. Is TG > 400 mg/dL?**

OBJECTIVE

To identify patients for whom LDL-C calculation is not reliable.

ANNOTATION

The Friedwald LDL calculation [LDL-C = total cholesterol - (HDL-C + TG/5) yields unacceptably inaccurate estimation of the LDL cholesterol in patients with triglycerides > 400. There are other means to measure atherogenic cholesterol in this setting. Non-HDL cholesterol can be estimated using the simple formula [Non-HDL cholesterol = Total cholesterol – HDL] or by direct measurement of the LDL.

DISCUSSION

LDL cholesterol reflects only a portion of the apo B-containing lipoproteins. VLDL, IDL, and lipoprotein are the other major forms of non-HDL cholesterol and are felt to possibly be as atherogenic as LDL particles. Also, LDL levels cannot be accurately calculated with Friedewald's formula when triglyceride levels exceed 400 mg/dL. Non-HDL-C has been advocated as a reasonable method for assessing total apo B-containing particles especially in cases complicated by the presence of hypertriglyceridemia. Technology that can directly measure LDL-cholesterol should be considered if available. Alternatively, one can use the non-HDL estimation approach.

Non-HDL cholesterol can be estimated by the simple formula:

Non-HDL cholesterol = Total cholesterol – HDL

Since non-HDL cholesterol levels tend to be approximately 30 mg/dL greater than estimated LDL levels, the estimated LDL from this equation will be approximately 30 points lower and LDL goals need to be interpreted accordingly. For example, if the goal LDL is <130 mg/dL, then the non-HDL cholesterol goal should be < 160 mg/dL instead. One can also continue to use specified guidelines for LDL levels if an adjusted version of the non-HDL cholesterol equation is followed:

Adjusted non-HDL cholesterol = (Total cholesterol – HDL) – 30 mg/dL

Of course, if triglyceride levels can be brought to < 400 mg/dL by dietary or other interventions, then Friedewald's formula can be used to calculate a more exact LDL-C level.

REFERENCE

Frost & Havel, 1998

**P. Is TG > 1000 mg/dL? Evaluate and Treat as Indicated**

OBJECTIVE

To identify and treat patients with extreme levels of triglycerides.

ANNOTATION

Patients with triglycerides >1,000 are at increased risk of pancreatitis.

DISCUSSION

The association between severe hypertriglyceridemia and pancreatitis is well recognized. The primary initial treatment is dietary with strict avoidance of alcohol and dietary fat, as well as restriction of calories. Secondary causes must be evaluated and treated as well. See Annotations M and N. Furthermore, pharmacologic therapy with a triglyceride-lowering drug should be considered if the values remain in the pancreatitis range despite a brief trial of the above therapy. Referral to a lipid specialist should be considered for resistant cases.

**Table 2. Treatment of Hypertriglyceridemia**

| Drug Therapy | First Choice | Alternative | Remarks |
|---|---|---|---|
| TG > 1000 mg/dL | Fibrates | Niacin | • Fibrates are contraindicated in severe renal disease<br>• Niacin is contraindicated in hepatic disease and relatively contraindicated in DM, gout, and history of complicated/active peptic ulcer disease (PUD). |

EVIDENCE

*Treat extreme levels of triglycerides*. (QE=III, SR=A). Piolot et al., 1996; NCEP III, 2001

**Q. Initiate Medical Nutrition Therapy (MNT) and Exercise**

OBJECTIVE

To reduce TG level with non-pharmacological therapy.

ANNOTATION

For those individuals with elevated TG, the clinician should initiate MNT (NIH Consensus Conference, 1993) and appropriate exercise program. See Appendix 1, MNT, and Appendix 2, Exercise.

DISCUSSION

Lifestyle modifications can significantly improve TG levels (Executive Summary, 1998). MNT can lead to significant decreases in total cholesterol, LDL-C, and TG (Sikand et al., 1998; Shafffer & Wexler, 1996; Shenberger et al., 1992). Many patients need more intense

dietary education to adequately modify their diet, usually a minimum of three to four months (Schenberger et al., 1992).

Researchers consistently demonstrate a dose-response relationship to ASCVD risk reduction and improved lipid profiles with increasing total activity time and caloric expenditure. In addition, it has been shown that diet and exercise have a synergistic effect when combined, and both aerobic and resistance training are helpful for improving dyslipidemia. Therefore, exercise and diet should be prescribed together, and the current exercise guidelines for the general population would also be beneficial for patients with dyslipidemia (Pate et al., 1995; Joint British recommendations, 1998).

EVIDENCE

*MNT*. (QE=III, SR=A). NIH Consensus Conference, 1993

*Exercise*. (QE=III, SR=A). NIH Consensus Conference, 1993; Pate et al., 1995; Joint British recommendations, 1998

**R. Is LDL-C > 160 mg/dL (Estimated Non-HDL-C > 190)?**

OBJECTIVE

To identify patients who may need therapy for hypercholesterolemia.

ANNOTATION

Patients with LDL cholesterol > 130 who have two or more atherosclerotic risk factors (other than cholesterol) or diabetes mellitus have significant risk of coronary or peripheral vascular events. Multiple prospective intervention trials have consistently demonstrated reduction in atherosclerotic event rates with treatment of hypercholesterolemia. In patients with known CHD (secondary prevention), the reduction in clinical endpoints is particularly compelling based on the demonstration of mortality benefit in some studies.

EVIDENCE

*LDL > 160 (Primary Prevention)*. (QE=I, SR=A). Downs et al., 1998; Helsinki Heart Study, 1987; The Lipid Research Clinics, 1984; Shepherd et al., 1995; NCEP III, 2001

**S. Determine Goal of Therapy; Initiate/Modify Therapy to Achieve Goal**

OBJECTIVE

To select an appropriate therapy based on LDL-C baseline level and other risk factors for ASCVD.

1. Select an appropriate LDL-C target
2. Initiate nonpharmacologic therapy
3. For patients who do not reach LDL target, initiate pharmacotherapy.

ANNOTATION

Treatment should be based on LDL-C and CHD risk. CHD risk factors are age, family history, current smoker, hypertension, diabetes, and HDL-C < 40 mg/dL. Patients with CHD or multiple risk factors require more aggressive treatment. The goals for therapy and treatment are summarized inTable 3b.

**Table 3a. LDL-C Thresholds for Initial Dyslipidemia Treatment**

| | **Baseline LDL-C [mg/dL]** | | | |
|---|---|---|---|---|
| **Risk for ASCVD** | **>100** | **>130** | **>160** | **>190** |
| Known CHD | Diet/exercise Consider drug | Diet/exercise + drug | Diet/exercise + drug | Diet/exercise + drug |
| Diabetes (without known CHD) | Diet/exercise Consider drug | Diet/exercise+ drug | Diet/exercise + drug | Diet/exercise + drug |
| No known CHD but > 2 risk factors | ____ | Diet/exercise | Diet/exercise + drug | Diet/exercise + drug |
| No known CHD but < 2 risk factors | ____ | ____ | Diet/exercise | Diet/exercise + drug |

Adapted from NCEP III, 2001
Note: If one risk factor is diabetes, the diabetes category is used to determine threshold and goal.

**Table 3b. LDL-C Goals in the Treatment of Dyslipidemia.**

| Risk for ASCVD | LDL-Cholesterol Goal |
|---|---|
| Known CHD | <120 mg/dl* |
| Diabetes (without known CHD) | <120 mg/dl* |
| No known CHD, but > 2 risk factors | <130 mg/dl |
| No known known, CHD, but ≤ 2 risk factors | <160 mg/dl |

*NCEP III recommends an LDL-C goal of < 100 mg/dL in patients with known CHD and CHD equivaltents (i.e., type 2 diabetes mellitus)

**Non-Pharmacologic Therapy**

Lifestyle change is indicated in all patients with 2 risk factors and LDL > 130mg/dL (> 100 mg/dL for known CHD or diabetes). Strategies include diet, exercise, smoking cessation, cessation of excessive alcohol, and weight control.
For primary prevention of ASCVD, patients whose initial treatment is diet/exercise should be given three to six months on dietary therapy prior to beginning medication, and longer if lipids are improving and nearing LDL thresholds. Patients failing clinician-initiated efforts may benefit from a MNT consult prior to initiating medications (See Appendix 1 for Medical Nutrition Therapy). The expected response to diet therapy is summarized in the following Table 4. For secondary prevention of recurrent ASCVD events, non-pharmacologic therapy is always indicated, but should not delay appropriate pharmacotherapy.

**Table 4. Expected Percent Change in Serum Lipids in Response to Diet Therapy**

| | **Expected Response to Therapy** | | | |
|---|---|---|---|---|
| | Step I Diet | Step II Diet | Very Low Fat | High MUFA[a] |
| LDL | -5 to -20 % | -10 to -25 % | -0 to -20 % | -5 to -20 % |
| TG | +5 to -10 % | +10 to -10 % | Decrease with weight loss<br>Increase without weight loss | No change or slight decrease |

[a]MUFA = Monounsaturated fatty acids.
Cardiovascular Nutrition, ADA, 1998

**Pharmacologic Therapy**

Drug therapy is indicated in CHD/ASCVD patients and moderate-high risk primary prevention patients who remain above LDL thresholds with non-pharmacologic measures. HMG-CoA reductase inhibitors (statins) are first line agents in most situations. They are cost-effective in secondary prevention and high-risk primary prevention risk groups. **The dose should be adjusted at 4 to 6 week intervals until the individually-determined LDL-C goals are met.** Other agents have been shown to reduce CHD events and angiographic progression, but have had minimal impact on total mortality. The first line drugs and alternatives for lipid disorders are summarized in Table 5.

**Table 5. Dyslipidemia Drug Therapy Recommendations**

| LIPID DISORDER | MONO THERAPY | EFFICACY | | CONSIDERATIONS |
|---|---|---|---|---|
| ↑ LDL-C | | LDL | | • Caution using statins in hepatic disease<br>• Niacin is contraindicated in hepatic disease and relatively contraindicated in DM, gout, and history of complicated/active PUD.<br>• Resins may increase TG |
| Initial | Statins | -22 to -60% | | |
| Alternate | Niacin | -13 to -21% | | |
| | Bile acid resin (resin) | -10 to -20% | | |
| ↑ LDL-C and ↑ TG | | LDL | TG | • For high TG, use fibrates or niacin<br>• For high LDL, use statins |
| Initial | Niacin | -13 to -21% | -10 to -24% | |
| | or statin | -22 to -60% | -06 to -37% | |
| Alternate | Fibrates | +10 to -35% | -32 to -53% | |
| ↑LDL and ↓ HDL | | LDL | HDL | • No preferences in terms of efficacy |
| | Niacin | -13 to -21% | +10 to +24% | |
| | or statin | -22 to -60% | +2 to +12% | |
| | or fibrates | +10 to -35% | +2 to +34% | |
| TG 400-1000 mg/dL | Consider gemfibrozil if HDL-C < 40 mg/dL[a] | | | • For high TG, use direct LDL-C measurement or non-HDL-C as lipid disorder to guide therapy |

Adapted from PBM-MAP, 1997.
[a]VA-HIT, 1999.

**For CHD/ASCVD Patients**

For patients with known CHD/ASCVD who have HDL < 40 mg/dL pharmacotherapy with gemfibrozil is recommended (VA-HIT, 1999)

| | | | | |
|---|---|---|---|---|
| LDL-C ≤ 130 mg/dL And HDL-C < 40 mg/dL | Gemfibrozil | LDL +10 to –35% | HDL +2 to 34% | • Outcome data for secondary prevention only |

Adapted from PBM-MAP, 1997.

## DISCUSSION

### Primary Prevention

Treatment should be based on risk, which varies widely in this group of patients. CHD risk increases with increasing risk factors (annotation B), and can be easily calculated (Wilson et al., 1998). Lowering cholesterol has been shown to reduce the incidence of CHD, with each 10 percent reduction dropping the incidence by 20 to 30 percent. However, in patients with low absolute risk for developing CHD, even this impressive relative risk reduction results in small change in the absolute risk or total event rate. The National Cholesterol Education Program guidelines recommend LDL targets of < 130mg/dL for two or more CHD risk factors, and < 160mg/dL for zero to one CHD risk factors.

Lifestyle changes are the first mode of treatment. This includes dietary changes, exercise, weight reduction, smoking cessation, and reduction of excessive alcohol. Dietary changes are an important first step in CHD risk reduction. However, the response in clinical practice is often substantially less than that seen in trials. Likewise, multiple risk factor reduction strategies have not yielded consistently improved lipids or outcomes (Ebrahim & Davey Smith, 1999). Patients should be given 3 to 6 months on dietary therapy prior to beginning medication, and longer if lipids are improving and nearing LDL thresholds. All patients failing clinician-initiated efforts should have a MNT consult prior to initiating medications.

Drug therapy should be reserved for those at increased CHD risk who fail to reach LDL targets with lifestyle modifications. Primary prevention trials with statins have demonstrated a reduction in CHD events and total mortality (in a high-risk population). Prior to statins, primary prevention trials had been shown to reduce CHD events, but not mortality. The AFCAPS/TexCAPS study examined outcomes in 5608 men and 997 women with average total cholesterol and LDL, and below average HDL (Downs et al., 1998). Patients randomized to lovastatin had 37 percent fewer first CHD events. The number needed to treat (NNT) to prevent one CHD event was 86. This was a relatively low risk population. The West of Scotland Study (WOSCPS) evaluated a higher risk population, and also found dramatic benefits from statin (pravastatin) treatment (Shepard et al., 1995). Over five years, CHD events were 31 percent lower, with significant reductions in CHD (32 percent) and total (22 percent) mortality. The NNT to prevent one nonfatal MI or CHD death was 42. Drug therapy was cost effective in the WOSCPS trial (about $12,000 per year of life saved), but it is unlikely that statins will be cost effective in lower risk populations at current pricing. This contrasts with the secondary prevention study (4S, 1994), which was cost effective in all age groups. There are no cost effectiveness studies with niacin in primary prevention, and it is unlikely that resins could be cost effective given their high cost per LDL reduction. Niaspan,

a new extended release niacin product, offers once-a-day dosing, and fewer side effects, but at a price comparable to statins.

**Secondary Prevention**

Secondary prevention refers to patients with known CHD or ASCVD. These individuals are at high risk for recurrent events. Lipid-lowering treatment has been shown to reduce CHD events, cardiac mortality, and total mortality in patients with CHD. Studies have shown that statins and niacin reduce stroke through secondary prevention. A systematic review found that peripheral vascular disease events were reduced as well (Leng et al., 1999). These patients have a high absolute risk for developing vascular events, and so derive significant absolute risk reduction in addition to relative risk reduction. Early trial data with non-statin drug therapy in CHD patients was disappointing. Lipid reductions were not dramatic, dropouts were high (due to side effects), and increases in non-CHD mortality and morbidity reduced overall benefit. Angiographic trials have shown that statins and other agents slow the progression of atherosclerosis as measured by serial coronary angiography. In the past five years, large randomized controlled trials with statins have shown that lipid lowering reduces both CHD and total mortality. Furthermore, the reduction in coronary events appears to be out of proportion to the slowing of atherosclerotic progression, suggesting that much of the benefit from statins occurs by another mechanism (e.g., "plaque stabilization").

Dietary counseling by primary care providers or MNT consultation is indicated if LDL >100mg/dL. Exercise must be tailored to the degree of CHD. Aerobic exercises should be titrated to a level that does not precipitate angina. Patients should exercise at least 30 minutes on most days of the week. How long to give lifestyle change before adding pharmacotherapy for dyslipidemia is unclear, but certainly less than in primary prevention.

- ***Initial Therapy:*** Evidence clearly supports initiation of pharmacotherapy when LDL is > 130 mg/dL in patients with CHD (4S, 1994). For CHD patients with HDL > 40 mg/dL and LDL < 130 mg/dL, there is insufficient evidence on which to base a recommendation for pharmacotherapy. Individual clinicians may choose to initiate drug therapy for LDL > 100mg/dL for secondary CHD prevention, based on consensus opinion. Of note, however, a prospective secondary prevention trial, the CARE study, found no outcomes benefit when high-dose pravastatin was initiated at a baseline LDL < 125mg/dL (Sacks, 1996).

- ***Choice of drug:*** The statins are the best studied and show most benefit, in terms of absolute LDL reduction and patient outcome. Older trials with niacin and bile acid resins have shown modest reduction in LDL (10 to 20 percent) and CHD event rates, with some evidence of small mortality benefit. Fibrates, which have minimal effect on LDL, have shown reduced CHD event rates, but not mortality (Rubins et al., 1999; Frick et al., 1987). Statin-based outcome trials have included lovastatin, pravastatin, and simvastatin. There is no convincing evidence that one statin is better than another. Choice and starting dose should be dictated by the required LDL reduction, as statins differ in their potency. The dose should be adjusted at six to eight week intervals until LDL reduction goal is achieved.

- ***Failure to reach LDL goal with statins***: Some patients will not achieve their LDL target with full dose statins. What should be done? It is not clear. Adding niacin/bile acid binding resins will further lower LDL, and may provide clinical benefit (Canner et al., 1986). Gemfibrozil will not substantially change the LDL, and so is not indicated in this situation. Until further evidence is available, the addition of niacin or resins could be considered. In combination with statins, niacin increases the risk of hepatitis and rhabdomyolysis, but will raise HDL and lower triglycerides. Frequent monitoring of liver function tests is prudent when combination therapy is used.

- ***Aggressiveness of LDL reduction***: There is no direct evidence from RCT's demonstrating a net benefit (in terms of clinically relevant endpoints) of treating to an LDL goal of less than 130 mg/dl. There is indirect evidence from the 4S Trial that in patients with previous CHD, treatment with simvastatin to an average LDL of 118 mg/dl, the benefits clearly outweighed harms. As noted above, NCEP III recommends lowering LDL to < 100 mg/dL in the secondary CHD prevention setting. Trials are now underway to determine whether even more aggressive treatment produces additional benefit. An angiographic trial in CABG patients showed that patients treated to a target LDL < 140mg/dL had worse outcomes than those treated more aggressively, to a target LDL < 85mg/dL (Post CABG Trial, 1997). After four years, angiographic progression for the aggressive and moderate groups was 27 percent and 39 percent, respectively. Revascularization was reduced by 29 percent in the lower LDL group. Some experts argue that it is the percentage drop in LDL, not the absolute LDL achieved that is important in achieving benefit. Treating to New Targets (TNT) is a five year RCT currently under way looking at lowering LDL to very low target levels in patients with CHD, who are randomizing to atorvastatin 10mg vs. 80mg per day. The results of the 4S Trial suggest that there may be additional benefits of lowering LDL to less than 130 mg/dl. Both the VHA/DoD working group for the management of dyslipidemia and the VHA/DoD working group for the management of ischemic heart disease recommend a treatment goal of < 120 mg/dL, while waiting for a more definitive answer.

**HDL Cholesterol < 40 mg/dl with LDL < 130 mg/dl**

Large epidemiologic trials have shown that a low HDL is associated with an increased risk for cardiovascular events (Gordon, 1989). In the VA-HIT trial (1999), patients with established cardiovascular disease, an HDL < 40 mg/dL and an LDL < 140 mg/dL were randomized to treatment with gemfibrozil vs. placebo. The mean entry HDL of the treatment arm was 32 mg/dL and the mean entry LDL level was 111 mg/dL. Following a mean follow-up of five years, the gemfibrozil treatment arm saw a 22 percent relative risk reduction in the combined end point of nonfatal myocardial infarction or death due to cardiovascular disease, and a 25% reduction in stroke. Subgroup analysis of VA-HIT strongly suggests that CHD patients with low HDL, triglycerides > 200 mg/dl, hypertension, or impaired fasting glucose were particularly likely to benefit from gemfibrozil therapy. The study was not powered to detect an overall mortality benefit.

For additional information see VHA/DoD guideline for IHD - Modules for Secondary Prevention and Cardiac Rehabilitation.

EVIDENCE

*Lifestyle education*. (QE=I, SR=A). Wilson et al., 1998; Ebrahim & Davey Smith, 1999

*Primary prevention*. (QE=I, SR=A). Downs et al., 1998; Shepard et al., 1995

*Secondary prevention*. (QE=I, SR=A). Scandanavian Simvastatin Survival Study Group (4S), 1994; Leng et al., 1999; NCEP III, 2001; Sacks et al., 1996; Frick et al., 1987; Canner et al., 1986; Post CABG Trial, 1997

*Treatment of low HDL*. (QE=1, SR=A). Gordon et al., 1989 Rubins et al., 1999

**T. Follow Up, Repeat Lipid Evaluation at Least Annually**

OBJECTIVE

To assure that patients initially treated for dyslipidemia receive periodic reassessment of the efficacy of treatment.

ANNOTATION

When dyslipidemia is identified and the care provider and patient undertake dietary and/or pharmacologic treatment, it is pertinent clinically and economically to periodically repeat measurement of serum lipids to ensure that initially desirable response to therapy continues. Total and LDL cholesterol tend to increase with advancing age, even in intensively treated patients. Thus, an initially favorable response to treatment may not be maintained over time.

DISCUSSION

New medical conditions, such as hypothyroidism, nephrotic syndrome, and diabetes mellitus, can appear at any time. The dyslipidemias associated with these conditions may exacerbate pre-existing primary hyperlipidemia and thwart previously effective dietary and/or pharmacologic therapy. Marked change in serum lipids may prompt timely diagnosis and treatment of such concurrent health conditions.

EVIDENCE

*Periodic follow up*. (QE=III, SR=B). NCEP III, 2001

## U. Address Adherence to Therapy

### OBJECTIVE

To address patient adherence to diet, exercise, and drug therapy.

### ANNOTATION

Patients should be questioned about adherence to treatment at each visit. A minimum of three to six months of intensive diet and exercise is recommended before medications are initiated for primary prevention. Shorter trials of MNT and exercise are appropriate for patients with severe hyperlipidemia or ASCVD, since aggressive drug therapy is of demonstrated efficacy in these high risk groups.

Reasons for medication noncompliance include the following:

1. Medication side effects: Particularly an issue for niacin and resins, although statins may cause myalgias and nonspecific gastrointestinal symptoms.

2. Incomplete patient education: Patients may not understand benefit of medication or need for long-term therapy.

3. Cost: Patients may not be able to afford medications.

Reasons for diet and exercise noncompliance include the following:

1. Incomplete patient effort and self-motivation: Some patients are unable or unwilling to comply with strict dietary changes, such as a Step II diet, and a regular exercise regimen.

2. Suboptimal social support: Family and lifestyle may not be conducive to strict dietary changes. Patients may not have access to exercise facilities or safe environment (e.g., safe neighborhood in which to walk).

3. Incomplete patient education: Some patients may not have received adequate information because of missed visits or inadequate time for counseling.

4. Cost: Patients may perceive that dietary interventions increase costs, though this is generally not the case. Patients unable to walk may not have access to other exercise options (swimming, stationary bike/machines, etc.).

### REFERENCE

Workgroup Communication: Lipid Editing Session, October 19, 1999.

**V. Modify Drug Therapy; Consider Combination Therapy**

OBJECTIVE

To modify drug therapy to achieve LDL-C goal.

ANNOTATION

Niacin and resins are considered alternative therapy in patients who do not tolerate initial therapy. If the patient has not achieved the LDL-C goal with initial therapy, consider the addition of a second agent. Clinical judgment must be used to balance patient issues, side effects, and monitoring parameters.

DISCUSSION

Niacin lowers TG and elevates HDL-C. Niacin is relatively contraindicated in patients with diabetes mellitus, as it may worsen glucose tolerance. Niacin may cause flushing, gastrointestinal disturbance, exacerbate peptic ulcer disease and gout, and may cause drug-related hepatitis. Niacin is contraindicated in patients with hepatic disease. Refer to Appendix 3 for drug interactions and 4 for prescribing information.

The addition of a resin may provide further LDL reduction. It may, however, increase TG levels. Resins can be used for hypercholesterolemic patients in need of modest LDL reduction or for patients unable to tolerate first-line agents.

Combining fibrates with statins may provide additional increases in HDL and reductions in TG. However, the potential benefit must be balanced against an increased risk of myopathy. Niacin combined with a statin also raises HDL and lowers TG levels. It is associated with an increased risk of myopathy; however, the risk is lower than with fibrates.

REFERENCE

PBM-MAP, 1997

**W. Reschedule Lipids Evaluation at Appropriate Time and Follow Up until Goal Met**

OBJECTIVE

To assure that the efficacy of prescribed therapy of hyperlipidemia is measured after allowing sufficient time to reach a new steady state.

ANNOTATION

Nadir values of LDL cholesterol and triglycerides may not be achieved until after three to six months on a Step I or Step II diet. Pharmacotherapy likewise may not result in lower lipid values until after at least one month of treatment. Remeasurement of serum lipids after at least one month of drug therapy, or after at least three months of dietary therapy, allows for

the documentation of efficacy, the identification of unfavorable effects of treatment, and the dose titration of medication.

DISCUSSION

Follow-up visits should include:

- Patient history, including compliance with nonpharmacologic measures such as diet, compliance with medication, need for changes in drug therapy regimen, presence of symptoms suggesting adverse drug reactions, adherence to exercise program if prescribed, and reevaluation of the modifiable cardiovascular risk factors.

- Physical exam, including weight and blood pressure, should be repeated as indicated by symptoms and severity of comorbid health condition.

- Laboratory tests, including periodic fasting lipid profile, and creatine kinase (CK) if symptoms of myopathy are present. For patients on gemfibrozil, statins, or niacin, transaminases (AST, ALT) are indicated at one- to three-monhth intervals initially, and at least every 6 to 12 months for patients on a stable maintenance regimen.

- Adverse events to be considered include: hyperglycemia, hyperuricemia (for patients on niacin), significant (> 3 times the upper limit of normal) elevations of transaminases (with niacin, statins, gemfibrozil) and myalgias (with gemfibrozil or statins).

REFERENCES

NCEP III, 2001; Lovastatin Study Groups I through IV, 1993; Jones, 1991

**X. Is LDL-C > 130 mg/dL or HDL-C < 40 mg/dL?**

OBJECTIVE

To identify patients with ASCVD who are candidates for aggressive treatment of hypercholesterolemia.

ANNOTATION

Patients with known ASCVD (secondary prevention) have significant risk of coronary or peripheral vascular events and are therefore candidates for aggressive lipid management. Multiple prospective intervention trials have consistently demonstrated reductin in atherosclerotic event rates with treatment of hypercholesterolemia. For this group, the reduction in clinical endpoints is particularly compelling, based on the demonstration of mortality benefit in some studies. In the major clinical trials published to date, actual LDL-C attained with statin therapy has ranged between 98 mg/dL and 118 mg/dL. As noted in Table 3, the target lipid levels in secondary CHD prevention are:

- LDL-C < 120 mg/dL* and
- HDL-C > 40 mg/dL.

*NCEP III and the American Diabetes Association guidelines support initiation of LDL-lowering therapy for patients with LDL in the 100-130 mg/dL range. Absolute risk reduction in CHD events for drug treatment initiated at this threshhold has not yet been established, except in the setting of HDL-C < 40 mg/dL (VA-HIT Study, 1999).

In the VA-HIT Study, the average LDL-C of treated patients was 112 mg/dL and the average HDL-C was 33 mg/dL.

*Aggressive treatment for patients with known ASCVD*. (QE=I, SR=A). Post CABG Trial, 1997; Sacks et al., 1996; LIPID, 1998: Rubin et al., VA-HIT, 1999.

**Y. Repeat Evaluation in 1 to 2 Years as Indicated**

OBJECTIVE

To assure that patients with CAD risk factors other than hyperlipidemia are carefully monitored for onset of hyperlipidemia.

ANNOTATION

Because total and LDL cholesterol tend to increase with advancing age, patients with initially borderline LDL values may evolve frankly elevated LDL with the passage of 1 year, or may develop concurrent health conditions (nephritic syndrome, hypothyroidism, diabetes mellitus) that can declare as hyperlipidemia. Patients known to be at high risk for CAD based on multiple risk factors other than hyperlipidemia are candidates for early and aggressive dietary and pharmacologic therapy; thus annual reevaluation of serum lipid status is prudent and cost-effective.

REFERENCES

NCEP III, 2001; Lovastatin Study Groups, 1993; Jones, 1991

# VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DYSLIPIDEMIA** IN PRIMARY CARE

## APPENDIX 1

**Appendix 1.**
**Medical Nutrition Therapy**

Medical Nutrition Therapy (MNT) is an initial, effective, and low-cost approach to the management of patients with hypercholesterolemia (McGehee et al., 1995). MNT is the clinical nutrition assessment and the provision of appropriate nutrition therapy by a registered dietitian or nutrition professional. A primary care clinician should refer the patient for MNT. It has demonstrated effectiveness for many diagnoses and has shown to be associated with a decrease in utilization of health services (The Cost of Covering MNT under TRICARE, 1998).

MNT includes review and analysis of a patient's medical and dietary history, lab values, and anthropometric values. It is the provision of appropriate nutrition therapy, to include skills training for the patient, diet modification and outcomes-based counseling. The benefits of MNT are lowered morbidity and progress towards positive health outcomes (DCCT, 1993; Sikand et al., 1996; Sikand et al., 1997).

MNT can lead to significant decrease in total cholesterol, LDL-C and TG (Sikand et al., 1998; Shaffer & Wexler, 1996; Shenberger et al., 1992). In one study, 34 of 67 patients receiving MNT avoided use of lipid medications, at an annual cost savings of $60,561; this study demonstrated significant serum cholesterol reduction and health care dollar savings with just three or four individualized MNT visits.

Often patients have multiple medical conditions, each with specific dietary recommendations. MNT is an inexpensive and safe intervention (McGehee et al., 1995; Brannon et al., 1997; Stinnett et al., 1996; Tosteson, et al., 1997; Sheills et al., 1999; Splett, 1996). MNT teaches patients how to incorporate appropriate foods into their current eating patterns, and how to make long-term diet changes. MNT integrates information on food, nutrients, and meal preparation—consistent with cultural background, socioeconomic status, and desired clinical outcomes—to provide appropriate care (Medical Nutritional Therapy, 1998).

Dietary change can significantly reduce total cholesterol and LDL-C, and when part of an intensive lifestyle change program, can slow the progression and may actually reverse the disease process (Haskell et al, 1994; Ornish et al., 1990). MNT is an intrinsic component of clinical practice and a shared responsibility of the health care team. In the current managed care environment, we must provide optimal health outcomes in the most economical way.

The MNT Protocol for Dyslipidemia recommends three to four sessions, of 30 to 60 minutes in length.

ADDITIONAL INFORMATION: The following guidelines are provided to assist those who do not have access to nutrition professionals for MNT.

The primary focus of diet therapy for the prevention and treatment of hypercholesterolemia is to progressively lower saturated fatty acids (SFAs) and cholesterol at an energy level that facilitates optimal weight management (See Table for Step I and Step II diets). Other diet modifications may be necessary for particular patient subgroups.

1. Consumption of a diet in accordance with the NCEP/AHA guidelines, starting with a Step I diet. In some individuals, a Step II diet may be indicated, (NIH Consensus Conference, 1993). For hypertriglyceridemia, the proportion of carbohydrate to fat is controversial. However, the effect is attenuated in the context of weight reduction and with the incorporation of high fiber foods, (Tillotson et al. 1997; NIH Consensus Conference, 1993).

2. Complex carbohydrate and fiber should be emphasized while restricting simple carbohydrate, (NIH Consensus Conference, 1993).

3. Weight reduction: Often weight loss can significantly decrease plasma lipids and increase HDL-C levels, (NIH Consensus Conference, 1993; NCEP II, 1993).

4. Restriction of alcohol: Small amounts can result in fluctuations in serum triglycerides and should therefore be restricted at least on a trial basis, (NCEP II, 1993).

**Medical Nutrition Therapy Prescriptions for High Blood Cholesterol**

| Nutrient | Step I Diet | Step II Diet |
|---|---|---|
| Total Calories | To achieve and maintain desirable weight | |
| Total Fat | 30% or less of total calories[a] | |
| Saturated Fatty Acids | 8-10% of total calories | < than 7% of total calories |
| Polyunsaturated Fatty Acids | Up to 10% of total calories | |
| Monounsaturated Fatty Acids | Up to 15% of total calories | |
| Carbohydrates | 55% or more of total calories | |
| Protein | Approximately 15% of total calories | |
| Cholesterol | Less than 300 mg/day | Less than 200 mg/day |

Adapted from NCEP II, 1993

[a] Often this guideline is misinterpreted to mean that each (single) food item should be less than 30 percent fat. The guideline applies to total calories eaten over several days. Applying the 30 percent rule to single food items would exclude many appropriate food choices. Although Step I and Step II diets are frequently referenced as initial therapies, individualization based on nutritional assessment, BMI, co-morbidities, lifestyle and lipid reduction goal is essential for appropriate care. Patients eat foods, not nutrients. The MNT prescriptions must be translated into foods to be meaningful for patients (see patient education references).

It is important to provide ongoing support and reinforcement to patients undertaking significant dietary changes. This can take several forms, including follow-up visits,

telephone calls, and postcards. It is important to encourage patients through the plateaus and regressions that occur as a normal part of efforts at long-term change (USDHHS, Clinician's Handbook, 1998).

**Examples of foods to choose or decrease for the NCEP Step I and Step II Diets**

| Food Group | Choose | Decrease |
|---|---|---|
| Lean meat, poultry, and fish<br>≤ 5-6 ounces per day | Beef, pork, lamb – lean cuts well trimmed before cooking<br><br>Poultry w/o skin<br><br>Fish, shellfish<br><br>Processed meats prepared from lean meats, e.g., lean ham, lean frankfurters, lean meat with soy protein or carrageen | Regular hamburger, fatty cuts of beef, spare ribs, organ meats<br><br>Poultry with skin, fried chicken<br>Fried fish, fried shellfish<br><br>Regular luncheon meat (bologna, salami, sausage, frankfurters) |
| Eggs<br>≤ 4 egg yolks per week, Step I<br>≤ 2 egg yolks per week, Step II | Egg whites, cholesterol-free egg whites | Egg yolks (if more than the recommended); includes eggs used in baking and cooking |
| Low-fat dairy products | Milk-Skim ½% or 1% fat (fluid, powdered, evaporated, buttermilk)<br><br>Yogurt – non-fat or low-fat yogurt or yogurt beverages | Whole milk, regular yogurt (fluid, evaporated, condensed), 2% milk, imitation milk<br><br>Whole milk yogurt |
| Dairy products | Cheese-low-fat natural or processed cheese<br><br>Low-fat or non-fat varieties, e.g., cottage cheese-low-fat, nonfat, or dry curd 0% to 2%)<br><br>Frozen dairy dessert – ice milk, frozen yogurt (low-fat or nonfat)<br><br>Low-fat coffee creamer<br>Low-fat or nonfat sour cream | Regular cheeses (American blue, Brie, cheddar, Colby, Edam, Monterey Jack, whole-milk mozzarella, Parmesan , Swiss), cream cheese, Neufchatel cheese<br><br>Cottage cheese (4% milkfat)<br><br>Ice cream<br><br>Cream, half & half, whipping cream<br>Non-dairy creamer, whipped topping, sour cream |
| Fats and Oils<br>≤ 6-8 teaspoons per day | Unsaturated oils – safflower, sunflower, corn, soybean, cottonseed, canola, olive, peanut | Coconut oil, palm kernel oil, palm oil |

| | | |
|---|---|---|
| | Margarines -made from unsaturated oils listed above, especially soft or liquid forms<br><br>Salad dressings – made with unsaturated oils, low-fat or fat-free<br><br>Seeds and nuts – peanut butter, other nut butters<br>Cocoa powder | Butter, lard, shortening, bacon fat, hard margarine<br><br>Dressings – made with egg yolk, cheese, sour cream, whole milk<br><br>Coconut<br><br>Milk chocolate |

| **Food Group** | **Choose** | **Decrease** |
|---|---|---|
| Breads and cereals | Breads-whole-grain bread, English muffins, bagels, buns, corn or flour tortilla<br><br>Cereal – oat, wheat, corn, multigrain<br><br>Pasta<br><br>Rice<br><br>Dry beans and peas<br><br>Crackers, low-fat – animal type, graham, soda crackers, breadsticks, melba toast<br><br>Homemade baked goods using unsaturated oil, skim or 1% milk, and egg substitute—quick breads, biscuits, cornbread muffins, bran muffins, pancakes, waffles | Bread in which eggs, fat, and/or butter are a major ingredient; croissants<br><br>Most granolas<br><br>High-fat crackers<br><br>Commercial baked pastries, muffins, biscuits |
| Soups | Reduced-or low-fat and reduced sodium varieties, e.g., chicken or beef noodle, minestrone, tomato, vegetable, potato, reduced-fat soups made with skim milk | Soup containing whole milk, cream, meat fat, poultry fat, or poultry skin |
| Vegetables<br>3-5 servings per day | Fresh, frozen, or canned, without added fat or sauce | Vegetables fried or prepared with butter, cheese, or cheese sauce |
| Fruits | Fruit-fresh, frozen, canned or dried | Fried fruit or fruit served with butter or cream sauce |

| | | |
|---|---|---|
| 2-4 servings per day | Fruit juice – fresh, frozen or canned | |
| Sweets and modified fat desserts<br><br>Use cautiously if weight loss is recommended or with hypertriglyceridemia | Beverages – fruit – fruit-flavored drinks, lemonade, fruit punch<br><br>Sweets – sugar, syrup, honey, jam, preserves, candy made without added fat (candy corn, gumdrops, hard candy), fruit flavored gelatin<br><br>Frozen dessert – low-fat and nonfat yogurt, ice milk, sherbet, sorbet, fruit ice, popsicles<br><br>Cookies, cake, pie, pudding – prepared with egg whites, egg substitutes, skim milk or 1% milk, and unsaturated oil or margarine; ginger snaps, fig and other fruit bar cookies, fat-free cookies, angel food cake | Candy made with milk chocolate, coconut oil, palm kernel oil, palm oil<br><br>Ice cream and frozen treats made with ice cream<br><br>Commercial baked pies, cakes, doughnuts, high-fat cookies, cream pies |

From USDHHS, Clinician's Handbook, 1998

Note: Careful selection of processed foods is necessary to stay within the sodium guideline (< 2400 mg).

These represent general guidelines, which will need to be individualized for patients based on lipid profile, co-morbidities, and treatment goals.

**Specific Foods as Non-pharmocologic Therapy**

Consumers and health care professionals alike are increasingly interested in the use of functional foods (nutritious foods that contain specific ingredients that aid with specific physiological functions). Consumers are interested in non-pharmocologic ways to prevent diseases. Below is a summary of the more recognized nutrients, their potential benefits, and practical application.

**Nutrients with Strong Supportive Clinical Evidence**

| Specific Food | Potential Benefit | Concerns | Practical Advice |
|---|---|---|---|
| Fish Oil and Fish Oil Supplements* | ↓ TG levels<br>Effects on other lipids variable<br>Protective against CVD<br>↓ thrombus formation | Monitor if on anticoagulant therapy<br>Fish oil capsules may contribute to vitamins A and D toxicity<br>Some preparations lack vitamin E; concern for oxidation<br>Capsules expensive | Eat fish at least once a week, especially varieties high in n-3 fatty acids (salmon, sardines, mackerel) |
| Plant Sterols and Stanols | Shown to ↓ LDL 10-20% | | Include plant stanol ester foods into daily diet, ***substituted*** for foods of similar fat content |

* GISSI, 1999

**Other Nutrients**

| Specific Food | Potential Benefit | Concerns | Practical Advice |
|---|---|---|---|
| Vitamin E | Reduces risk of CVD<br>Reduces platelet aggregation<br>Reduces thrombus formation<br>Prevents unwanted oxidation | Caution with anticoagulant therapy<br>Difficult to obtain therapeutic amounts via foods alone | 400-800 IU/day appears safe<br>Food sources include vegetable oils, dark green leafy vegetables, nuts, avocados, whole grain cereals, fortified cereals |
| Beta Carotene (most abundant and biologicall | Anti-oxidant properties | High doses may discolor skin<br>Extent of risk reduction still unclear | Advise patients to get beta carotene via diet, consuming at least 5 servings of fruits/vegetables, especially leafy green and yellow |

| | | | |
|---|---|---|---|
| biologicall y active carotenoid) | | | vegetables (spinach, kale, carrots, yellow squash, broccoli) |
| Vitamin C | Works with vitamin E and beta carotene to prevent cellular oxidation<br>Effectiveness in decreasing risk of CVD is questionable | May cause abdominal bloating and diarrhea have been reported if > 2 g are consumed | Optimal intake difficult to assess, although probably in range of 180-750 (mg). Best food sources include citrus fruits, strawberries, broccoli, green peppers, tomatoes and potatoes |

| Specific Food | Potential Benefit | Concerns | Practical Advice |
|---|---|---|---|
| Soy Protein | Phytoestrogens in soybeans appear to reduce arthogenicity of LDL | No large multi-center, long-term clinical studies have tested safety nor effectiveness, although FDA has recently approved health claim for soy protein: "25 grams of soy protein per day may reduce risk of heart disease" | Low-fat soy foods are appropriate addition, especially if high cholesterol.<br>Food sources include tofu, soybeans, soynuts, soy milk, and soy cheese |
| Garlic | Modest reduction cholesterol, LDL-cholesterol, and TG<br>Antithrombotic properties | Considerable variability across studies<br>Can't identify who and what conditions would benefit most<br>Odor | Prudent to recommend eating a variety of foods and not to restrict garlic intake |

From Medical Nutrition, 1998

References for Tables:

1.Cater, N. B. (1999). Plant stanol ester foods: new tools in the dietary management of cholesterol. Nutrition and the MD, 25(11)

2. Merritt, R. J. (1999). Soy Protein Health Claim Gets FDA Authorization. Nutrition and the MD, 25(11)

References for patient education/nutrition/self-management programs:

3. The American Dietetic Association's Nationwide Nutrition Network is a national referral service that links consumers, physicians, food manufacturers, distributors or restaurant owners or managers with registered dietitians. All Participants in the American Dietetic Association's Nationwide Nutrition Network (dietitian referral service) are registered

dietitians—professionals who provide reliable, objective nutrition information, separate facts from fads and translate the latest scientific findings into easy-to-understand nutrition information. The web site address is http://www.eatright.org/find.html.

# Appendix 1
## Bibliography

Abstracts of Clinical Care Guidelines. (1997). The Joint Commission on Accreditation of Healthcare Organizations, 8(5), 1-8, 14-15.

American College of Physicians (ACP). (1996). Guidelines for using serum cholesterol, high-density lipoprotein cholesterol, and triglyceride levels as screening tests for preventing coronary heart disease in adults. Part 1. Annals of Internal Medicine, 124(5), 515-517.

Brannon, S. D., Tershakovec, A. M., Shannon, B. M. (1997). The cost-effectiveness of alternative methods of nutrition education for hypercholesterolemic children. American Journal of Public Health,87(12), 1967-1970.

Caggiula, A. W., Watson, J. E., Kuller, L. H., Olson, M. B., Milas, N. C., Berry, M. & Germanowski, J. (1996). Cholesterol-lowering intervention program. Effect of the Step I diet in community office practices. Archives of Internal Medicine,156(11), 1205-1213.

Cater, N. B. Plant stanol ester foods: new tools in the dietary management of cholesterol. (1999). Nutrition and the MD,25(11).

Diabetes Control and Complications Trial Research Group (DCCT). (1993). The effect of intensive treatment of diabetes on the development and progression of long-tern complications in insulin-dependent diabetes mellitus. New England Journal Medicine, 329, 977-986.

Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. (1999). Lancet, 354(9177), 447-455.

GISSI. See Dietary supplementation

Gosselin, P., Verreault, R., Gaudreault, C., & Guillemette, J.(1996). Dietary treatment of mild to moderate hypercholesterolemia. Effectiveness of different interventions. Canadian Family Physician, 42, 2160-2167.

Haskell, W. L., Alderman, E. L., Fair, J. M., Maron, D. J., Mackey, S. F., Superko, H. R., Williams, P. T., Johnstone, I. M., Champagne, M. A., & Drauss, R. M. (1994). Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease. Circulation, 89(3), 975-990.

Hebert, J. R., Ebbeling, C. B., Ockene, I. S., Ma, Y., Rider, L., Merriam, P. A., Ockene, J. K., & Saperia, G. M. (1999). A dietitian-delivered group nutrition proram leads to reduction in dietary fat, serum cholesterol, and body weight: The Worcester Area Trial for Counseling in Hyperlipidemia (WATCH). Journal of the American Dietetic Association. 99(5), 544-552.

Kris-Etherton, P. & Burns, J. (eds). (1998). Cardiovascular Nutrition: Strategies and Tools for Disease Management and Prevention. American Dietetic Association, Chicago, IL.

Lindholm, L. H., Ekbom, T., Dash, C., Eriksson, M., Tibblin, G. & Schersten, B. (1995). The impact of heatlh care advice in primary care on cardiovascular risk. CELL study Group. British Medical Journal.;310 (6987), 1105-1109.

McGehee, M. M., Johnson, E. Q., Rasmussen, H. M., Sahyoun, N., Lynch, M. M. & Carey, M. (1995). Benefits and costs of medical nutrition therapy by registered dietitians for patients with hypercholesterolemia. Journal of the American Dietetic Association. 95(9),1041-1043.

Medical Nutrition Across the Continuum of Care. (1998). Second Edition. The American Dietetic Association, Chicago, IL.

Merritt, R. J. (1999). Soy Protein Health Claim Gets FDA Authorization. Nutrition and the MD. 25(11).

National Cholesterol Education Program (NCEP). Second report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). NIH Publication No. 93-3095, National Institutes of Health, National Heart, Lung, and Blood Institute, Bethesda, MD, 1993.

NIH Consensus Conference: Triglyceride, High-Density Lipoprotein, and Coronary Heart Disease. (1993). Journal of the American Medical Association. 269(4), 55-100.

OASD(HA) Policy 97-055. Memorandum for Surgeons General: Policy for Medical Nutrition Therapy (MNT) in Direct Care Clinical Practice, 1997

Ornish, D., Brown, S. E., Scherwitz, L. W., Billings, J. H., Armstrong, W. T., Porta, T. A., McLanahan, S. M., Kirkeeidee, R. L., Brand, R. J., & Gould, K. L. (1990). Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. Lancet. 336:129-133.

Shaffer, J. & Wexler, L. F. (1996). Reducing low-density lipoprotein cholesterol levels in an ambulatory care system. Results of a multidisciplinary collaborative practice lipid clinic compared with traditional physician-based care. Archives of Internal Medicine, 156(13), 1476-1479.

Sheills, J. F., Rubin, R., & Stapleton, D. C. (1999). The estimated costs and savings of medical nutrition therapy: the Medicare population. Journal of the American Dietetic Association.99,428-432.

Shenberger, D. M., Helgren, R. J., Peters, J. R., Quiter, E., Johnston, E. A., & Hunninghake, D. B. (1992). Intense dietary counseling lowers LDL cholesterol in the recruitment phase of a clinical trial of men who had coronary artery bypass grafts. Journal of the American Dietetic Association. 92(4), 441-445.

Sikand G, et al. (1996). Beneficial outcome and cost savings with medical nutrition therapy by registered dietitians in hypercholesterolemia. Journal of the American Dietetic Association. 9 Supplement:A-13.

Sikand, G., Kashyap, M. L., Yang, I. (1998). MNT lowers serum cholesterol and saves medication costs in men with hypercholesterolemia. Journal of the American Dietetic Association. 98(8):889-898.

Sikand, G., et al. (1997). Beneficial lipid outcome of medical nutrition therapy for men with combined hyperlipidemia in an ambulatory setting. Journal of the American Dietetic Association 9. Supplement:A-11.

Splett, P. L. (1996). Cost Outcomes of Intervention: Economic and Cost Analysis of Nutrition Intervention, Part 3. Evansville, IN: Mead Johnson & Company.

Stinnett, A. A., Mittleman, M. A., Weinstein, M. C., Kuntz, K. M., Cohen, D. J., Williams, L. W., Goldman, P. A., Staiger, D. O., Hunink, M. G. M., Tsevat, J., Tosteson, A. N. A., & Goldman, L. The Cost Effectiveness of Dietary and Pharmacologic Therapy for Cholesterol Reduction in Adults. In: Gold, M. R., Siegal, J. E., Russell, L. B., & Weinstein, M. C. (eds). (1996). Cost Effectiveness in Health and Medicine. First Edition. New York: Oxford University Press.

The Cost of Covering Medical Nutrition Therapy Services under TRICARE: Benefit Costs, Cost Avoidance and Savings, The Lewin Group, Inc., 1998.

Tillotson, J. L., Grandits, G. A., Bartsch, G. E. & Stamler, J. (1997). Relation of dietary carbohydrates to blood lipids in the special intervention and usual care groups in the multiple risk factor intervention trial (MRFIT). American Journal of Clinical Nutrition.65(supplement):314S-26.

Tosteson, A. N. A., Weinstein, M. C., Hunink, M. G. M., Mittleman, M. A., Williams, L. W., Goldman, P. A., Goldman, L. (1997). Cost-effectiveness of population wide educational approaches to reduce serum cholesterol levels. Circulation;95:24-30.

U.S. Department of Health and Human Services. Public Health Service. (1998). Clinician's Handbook of Preventive Services: Put Prevention into Practice. Second Edition.

U.S. Preventive Services Task Force. (1996). Guide to Clinical Services Preventive Services. Second Edition. Alexandria, Virginia: International Medical Publishing.

# VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DYSLIPIDEMIA** IN PRIMARY CARE

## APPENDIX 2

# Appendix 2
# Exercise

Most studies demonstrate that an exercise program serves as a valuable nonpharmacologic means of improving lipid profiles in patients with dyslipidemia (including those with concurrent CHD/CVD, and/or DM). [2-6,8,10-11,20] Exercise parameters explored vary considerably, and researchers have yet to establish the exact levels for maximally increasing HDL, lowering LDL and triglycerides, and for slowing or reversing coronary atherosclerosis.[1,3-7,10-11,13,15,18,20,23-24] Researchers consistently demonstrate a dose response relationship to CHD/CVD risk reduction and improved lipid profiles with increasing total activity time and caloric expenditure[1,7,13,19,23-24]

Additionally, it has been shown that diet and exercise have a synergistic effect when combined, and both aerobic and resistance training are helpful for improving dyslipidemia.[2-4,9] Therefore, exercise and diet should be prescribed together, and the current exercise guidelines for the general population would also be beneficial for patients with dyslipidemia (with/without DM and/or CHD/CVD). [2-6,8-9,11,22,24]

The following specific exercise guidelines have not been assessed in a well-designed study to see if they produce the absolute optimal impact on dyslipidemia management but are a synthesis of various studies, prior exercise consensus panels, and an effort to use the positive dose relationship of exercise in improving dyslipidemia.[6-7,12-13,15,22,24]

The exercise guideline goal is to accumulate 30 minutes or more of moderate intensity physical activity on most (and preferably all) days of the week.[14,17-18,24] In addition to the aerobic component (complete with stretching and proper warm-up/cool), studies demonstrate that all patients could benefit from adding resistance training to their routine. The following are recommended: 2-3 sets of 8-12 repetitions, moderate weight, of at least 8-10 major muscles, 2-3 times per week.[15-16] Exercise testing and risk stratification may be appropriate when sedentary individuals over the age of 40 with CHD/CVD risk factors or established disease first begin an exercise program.[25,29] Recent studies show that such patients can ultimately progress to the same goals, if exercise is titrated appropriately—below symptomatic threshold, and with supervision (if indicated). [26-28,30]

Attached is an example of a handout that may help to encourage participation in the prescribed exercise program. Consider referring patients to a physical therapist or to a cardiac rehabilitation program when monitoring or supervision is indicated. [21,27] (See also VHA/DoD Guideline for IHD - Cardiac Rehabilitation Module)

**Exercise Handout**

How to improve your health, cardiovascular fitness and reduce body fat

| What can being physically active do for you? |
|---|

Here are some of the specific benefits of regular physical activity:

| | |
|---|---|
| **Heart Health:** | Can cut the risk of heart disease almost in half, and also may help prevent major risk factors, such as obesity and high blood pressure. |
| **Cholesterol Control:** | Can improve blood cholesterol profiles by raising HDL levels (good cholesterol) and lowering triglycerides, another fat carried in the blood. |
| **Muscling Out Fat:** | Improves the body's muscle-to-fat ratio by building or preserving muscle fat mass, which, in turn, increases calorie-burning efficiency to reduce body fat. |
| **Bone Support:** | Seems to slow the bone loss associated with advancing age—a major cause of fractures in later life. |
| **Insulin Enhancement:** | Enables the body to use insulin more efficiently, helping to control adult-onset diabetes. |
| **Cancer Check:** | By combating obesity, appears to lower the risk of certain cancers, particularly cancers of the breast, colon and uterus. |
| **Aerobic Improvement:** | Slows the decline in aerobic capacity (the maximum volume of oxygen the body can consume) that is associated with aging, helping to improve cardiorespiratory health. |
| **Weight Control:** | When combined with proper nutrition, can help control weight and prevent obesity, a major risk factor for many diseases. |
| **Attitude Adjustment:** | Reduces anxiety and depression, improves self-esteem, and helps you better manage stress. |

# Appendix 2

## Bibliography and Evidence Grading

1. Marrugat, J., Roberto, E., Covas, M. I., Molina, L., Rubies-Prat, J. & the MARATHON investigators. (1996). Amount and intensity of physical activity, physical fitness, and serum lipids in men. American Journal of Epidemiology. 143(6), 562-569. QE=II-2 SR=B

2. Stefanick, M., Mackey, S., Sheehan, M., Ellsworth, N., Haskell, W. L., & Wood, P. D. (1998). Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol. New England Journal of Medicine. 339(1), 12-20. QE=I SR=A

3. Ornish, D., Brown, S. E., Scherwitz, L. W., Billings, J. H., Armstrong, W. T., Ports, T. A., McLanahan, S. M., Kirkeeide, R. L., Brand, R. J., & Gould, K. L. (1990). Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial Lancet. 336(8708), 129-133. QE=I SR=A

4. Halle, M., Berg, A., Garwers, U., Baumstark, M. W., Knisel, W., Grathwohl, D., Konig, D., & Keul, J. (1999). Influence of 4 weeks' intervention by exercise and diet on low-density lipoprotein subfractions in obese men with type 2 diabetes. Metabolism. 48(5), 641-644. QE=II-2 SR=A

5. Mertens, D. J., Kavanagh, T., Campbell, R. B., & Shephard, R. J. (1998). Exercise without dietary restriction as a means to long-term fat loss in the obese cardiac patient. Journal of Sports Medicine and Physical Fitness. 38(4), 310-316. QE=III SR=B

6. Depres, J. P., & Lamarche, B. (1994). Low-intensity endurance exercise training, plasma lipoproteins and the risk of coronary heart disease. Journal of Internal Medicine. 236(1), 7-22. QE=I SR=B

7. Lakka, T.A., Venalainen, J. M., Rauramaa, R., Salonen, R., Tuomilehto, J., & Salonen, J. T. (1994). Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction. New England Journal of Medicine. 330, 1549-1554. QE=II-3 SR=A

8. Vasankari, T. J., Kujala, U. M., Vasankari, T. M., & Ahotupa, M. (1998). Reduced oxidized LDL levels after a 10-month exercise program. Medical Science in Sports Exercise. 30(10), 1496-1501. QE=II-3 SR=B

9. Thompson, P. D., Yurgalevitch, S. M., Flynn, M. M., Zmuda, J. M., Spannaus-Martin, D., Saritelli, A., Bausserman, L., & Herbert, P. N. (1997). Effect of prolonged exercise training without weight loss on high density lipoprotein metabolism in overweight men. Metabolism. 46(2), 217-223. QE=II-3 SR=B

10. Hartung, G. H., Squires, W. G., & Gotto, A. M. (1981). Effect of exercise training on plasma high-density lipoprotein cholesterol in coronary disease patients. American Heart Journal, 101(2),181-184. QE=II-3 SR=B

11. Maines, T. Y., Lavie, C. J., Milani, R. V., Cassidy, M. M., Gilliland, Y. E., & Murgo, J. P. (1997). Effects of Cardiac Rehabiliation and exercise programs on exercise capacity, coronary risk factors, behavior, and quality of life in patients with coronary artery disease. Southern Medical Journal. 90(1), 43-49. QE=II-2 SR=B

12. Prabhakaran, B., Dowling, E. A., Branch, J. D., Swain, D. P., & Leutholtz, B. C. (1999). Effects of 14 weeks of resistance training on lipid profile and body fat percentage in premenopausal women. British Journal of Sports Medicine. 33, 190-195. QE=I SR=A

13. American College of Sports Medicine Position Stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. Medical Science and Sports Exercise. 30(6), 975-991. QE=II SE=A

14. American College of Sports Medicine (ACSM) Guidelines for Exercise Testing and Prescription, Fifth Edition. Philadelphia: Williams & Wilkins, 1995. Pg. 162. QE= II-2 SR=A

15. Fletcher, G. (1997). How to implement physical activity in primary and secondary prevention. A statement for healthcare professionals from the task force on risk reduction, American Heart Association. Circulation 96, 355-357. QE=III SR=B

16. American College of Sports Medicine (ACSM) Guidelines for Exercise Testing and Prescription, (1995). Fifth Edition. Philadelphia: Williams & Wilkins.p. 174. QE= III SR=B

17. Pollock, M. L., & Wilmore, J. H. (1990). Exercise in Health and Disease: Evaluation and Prescription for Preventiontion and Rehabilitation, Second Edition. Philadelphia: WB Saunders. QE=III SR=B

18. Spate-Douglas, T. & Keyser, P. E. (1999). Exercise intensity: its effect on the high-density lipoprotein profile. Archives of Physical Medicine and Rehabilitation. 80, 691-695. QE=I SE=B

19. Wei, M., et al. (1997). Changes in lipids associated with change in regular exercise in free-living men. Journal of Clinical Epidemiology. 50(10), 1137-1142. QE=II-2 SE=B

20. Wood, P. D., Haskell, W. L., Blair, S. N., Williams, P. T., Krauss, R. M., Lindgren, F. T., Albers, J. J., Ho, P. H., & Farquhar, J. W. (1983). Increased exercise level and plasma lipoprotein concentrations: A one-year randomized, controlled study in sedentary middle-aged men. Metabolism. 32, 31-39. QE=I SR=A

21. Vongvanich, P. & Merz, N. (1996). Supervised exercise and electrocardiographic monitoring during cardiac rehabilitation. Journal of Cardiopulmonary Rehabilitation. 16, 233-238. QE=II-3 SR=B

22. Fletcher, G. F., Balady, G., Blair, S. N., Blumenthal, J., Caspersen, C., Chaitman, B., Epstein, S., Sivarajan Froelicher, E. S., Froelicher, V. F., Pina, I. L., & Pollock, M. L. (1996). Statement on exercise: Benefits and recommendations for physical activity programs for all Americans. Circulation. 94, 857-62. QE=III SR=B

23. Stein, R. A., Michielli, D. W., Glantz, J. D., Sardy, H., Cohen, A., Goldberg, N., & Brown, C. D. (1990). Effects of different exercise training intensities on lipoprotein cholesterol fractions in healthy middle-aged men. American Heart Journal. 119(2):277-283. QE=I SE=A

24. Pate, R. R., Pratt, M., Blair, S. N., Haskell, W. L., Macera, C. A., Bouchard, C., Buchner, D., Ettinger, W., Heath, G. W., King, A. C. (1995). Physical activity and Public Health. A recommendation from the Center for Disease Control and Prevention and the American College of Sports Medicine. Journal of the American Medical Association. 273, 402-407. QE= I SR=A

25. American College of Sports Medicine (ACSM) Guidelines for Exercise Testing and Prescription, (1995). Fifth Edition. Philadelphia: Williams & Wilkins. pg.8-26. QE= III SR=C

26. McConnell, T. R., Klinger, T., Gardner, J., Laubach, C., Herman, C., & Hauck, C. (1998). Cardiac rehabilitation without exercise tests for post-myocardial infarction and post-bypass surgery patients. Journal of Cardiopulmonary Rehabilitation. 18, 458-463. QE=I SR=B

27. Beniamini, Y, Rubenstein, J. J., Faigenbaum, A. D., Lichtenstein, A. H., & Crim, M. C. (1998). High-intensity strength training of patients enrolled in an outpatient cardiac rehabilitation program. Journal of Cardiopulmonary Rehabilitation. 19(1), 8-17. QE=I SR=A

28. McConnell, T. R. (1996). Exercise Prescription when the guidelines do not work. Journal of Cardiopulmonary Rehabilitation. 16, 34-37. QE=III SR=C

29. Thompson, P. D., Funk, E. J., Carleton, R. A., & Sturner, W. Q. (1982). The incidence of death during jogging in Rhode Island from 1975 through 1980. Journal of the American Medical Association. 247, 2535-2538. QE=III SR=B

30. Stewart, K. J., McFarland, L. D., Weinhofer, J. J., Cottrell, E., Brown, C. S., Shapiro, E. P. (1998). Safety and efficacy of weight training soon after acute myocardial infarction. Journal of Cardiopulmonary Rehabilitation. 18, 37-44. QE=I SR=A

# VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DYSLIPIDEMIA** IN PRIMARY CARE

## APPENDIX 3

## Appendix 3
## Drug Interactions with Bile Acid Resins, Fibrates, and Niacin[1]

The combination of a bile acid resin and statin can further the lipid-lowering potential of each agent. Combining fibrates with statins may provide additional increases in HDL-C and reductions in TG; however, the potential benefit must be balanced against an increased risk of myopathy.

Niacin combined with a statin also raises HDL-C and lowers triglycerides. It is associated with an increased risk of myopathy; however, the risk is lower than with fibrates. The niacin or statin product selected, as well as the dose of the statin, may affect the risk for myopathy.

| INTERACTIVE AGENT(S) | | CLINICAL MANIFESTATIONS |
|---|---|---|
| Bile acid resins (resins)<br><br>Cholestyramine<br>Colestipol | Digoxin<br>Levothyroxine<br>Warfarin | May decrease the absorption of many drugs; take other drugs 1 hour before or 4 hours after resin<br>May impair absorption of fat soluble vitamins |
| | Amiodarone | May increase the elimination of amiodarone; follow for increased dosage requirements of amiodarone |
| Fibrates<br>Fenofibrate<br>Gemfibrozil<br><br>(May also occur with clofibrate) | Glyburide | May cause hypoglycemia; may occur with other sulfonylureas |
| | Statin | Myopathy including rhabdomyolysis reported in up to 5% of lovastatin patients[2]; interaction also reported with atorvastatin[3] and cerivastatin[4]<br>Avoid combination if patient is on another agent that can affect CYP3A4 metabolism<br>Check pretreatment ALT<br>Monitor for musculoskeletal symptoms (CK normal range 21-235 U/L[5], look for 10x upper limit if patient is symptomatic) |
| | Warfarin | Risk of ↑ anticoagulant activity |
| Niacin | Statins | Myopathy reported in 2% of lovastatin patients with or without rhabdomyolysis may depend on niacin[6] and statin product selection (interaction is not reported with niacin and pravastatin[7])<br>Caution if patient is on another agent that can affect CYP3A4 metabolism |

| INTERACTIVE AGENT(S) | | CLINICAL MANIFESTATIONS |
|---|---|---|
| | | Check pretreatment ALT; recheck after initiation and dosage changes<br>Monitor for musculoskeletal symptoms |
| Statins | Azole antifungals (fluconazole, ketaconazole, itraconazole) | Decreases metabolism of statins, may increase myopathy (no reports with pravastatin) |
| | Immunosuppressives (cyclosporin, tacrolimus) | Increase risk of myopathy (not reported with fluvastatin or pravastatin) |
| | Macrolide antibiotics (clarithromycin, erythromycin) | Increase risk of myopathy (not reported with pravastatin) |
| | Protease inhibitors (ritonavir) | Increase the risk of myopathy (not reported with pravastatin or fluvastatin) |
| | Anticoagulants | Case reports of increased INR |
| | Niacin/Fibrates | Increased risk of myopathy |
| | Calcium channel blockers (diltiazem, verapamil) | Increased risk of myopathy |

**THIS TABLE INCLUDES SIGNIFICANT DRUG INTERACTIONS (TO DATE) AND MAY NOT ENCOMPASS ALL POSSIBLE AGENTS**

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[1] Bays, H., Dujovne, C. (1998). Drug interactions of lipid lowering drugs. Drug Safety. 19(5), 355-371.
Farmer, J. A., Gotto, A. M. (1994). Antihyperlipidaemic agents: Drug interactions of clinical significance. Drug Safety. 11(5), 301-309.
Garnett, W. R. (1995). Interactions with hydroxymethylglutaryl-coenzyme A reductase inhibitors. American Journal of Health-Systems Pharmacy. 52, 1639-1645.
Hansten, P. D., & Horn, J. R. (1997). Drug Interaction Analysis and Management. Vancouver: Applied Therapeutics.

[2] Garnett, W. (1995). Interactions with hydroxymethylglutaryl-coenzyme A reductase inhibitors. American Journal of Health-Systems Pharmacy.52, 1639-1645.

[3] Duel, P. B., Connor, W. E., & Illingworth, D. R. (1998). Rhabdomyolysis after taking atorvastatin with gemfibrozil. American Journal of Cardiology. 81, 368-9.

[4] Pogson, G. W., Kindred, L. H., & Carper, B. G. (1999). Rhabdomyolysis and renal failure associated with cerivastatin-gemfibrozil combination therapy. American Journal of Cardiology. 83, 1146.

[5] CK normal range may vary among laboratories, and is affected by age, race, exercise/muscle mass, and comorbid conditions.

[6] Guyton, J. R., & Capuzzi, D. M. (1998). Treatment of hyperlipidemia with combined niacin-statin regimens. American Journal of Cardiology. 82, :82U-84U.

[7] Curtis, A., ed. (1999). Physicians' Desk Reference. 53rd ed. Montvale, NJ: Medical Economics Company.

# VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DYSLIPIDEMIA** IN PRIMARY CARE

## APPENDIX 4

## Appendix 4
## Drug Therapy Summary [1, a-d]

| DRUG | LDL-C | HDL-C | TG | DOSE | CAUTIONS/MONITOR[e] |
|---|---|---|---|---|---|
| Resin<br>Cholestyramine<br>4 g powder/LIGHT colestipol<br>5 g powder/1 g tablet | ↓ 10-20%[f] | ± 3%[b] | ↑ 3-10%[b] | • Best tolerated 2-5 g bid; usual effective dose 8-10 g/d<br>• Take other meds 1 h prior or 4 h after or take with dinner | • May ↑ TG<br>• Caution if active PUD due to GI irritation |
| Niacin<br><br>100, 250, 500 mg IR tablet<br><br>IR at 1.5-3g/day<br><br>500 mg, 750 mg, 1 g ER tablets<br><br>ER at 1.5 g/day[g] | ↓ 13-21%<br><br>↓ 13% | ↑ 10-24%<br><br>↑ 19% | ↓ 19-24%<br><br>↓ 10% | • Start IR 50-100 mg bid-tid & ↑ dose by 300 mg/d per week (refer to Appendix 3 for *NIACIN DOSE PACK*); ER use titration pack<br>• Usual maximum daily dose IR 3 g/d; ER 1.5 g/d<br>• Take w/meals to avoid flushing or GI upset | • ALTs baseline, 6 weeks after start or dosage change; monitor every 6-12 months thereafter<br>• Causes glucose intolerance - caution in established or borderline DM<br>• May cause GI intolerance, caution w/ history of complicated/active PUD<br>• Decreases urinary secretion of uric acid, caution with gout<br>• Contraindicated in hepatic disease<br>• If CrCl is 10-50 ml/min give 50% of dose; if <10 ml/min give 25%[h] |
| Fibrates<br><br>Gemfibrozil<br><br>600 mg tab | +/- 10%[i] | ↑ 10%[i] | ↓ 43%[i] | • 600 mg bid | • Monitor ALTs throughout therapy; contraindicated in hepatic disease<br>• Reduce dose in modest renal insufficiency<br>• Risk of myopathy with statin<br>• Monitor INR; may need to adjust Warfarin dosage to prevent bleeding complications |
| fenofibrate<br>67 mg capsule | ↓ 17-35%[j] | ↑ 2-34%[j] | ↓ 32-53%[j] | • 67-201 mg/d | |
| Statins<br><br>atorvastatin 10, 20, 40 mg<br>certivastatin 0.2, 0.3, 0.4 mg<br>fluvastatin 20, 40 mg<br>lovastatin 10, 20, 40 mg tab<br>simvastatin<br>5, 10, 20, 40, 80 mg tab | ↓ 22-60%[k] | ↑ 2-12%[k] | ↓ 6-37%[k] | • Cerivastatin (DoD BCF agent 0.2-0.4 mg/day q p.m.)<br>• Lovastatin (VA National Formulary agent) 10-80 mg/day q p.m. (80 mg given as 40 mg BID)<br>• Simvastatin (DoD BCF/VA National Formulary agent) 5-80 mg/day q p.m.<br>• Evening/bedtime dosing may improve efficacy | • ALTs ↑ in 0.1-1.9%[l]; monitor ALT within 3 months of initiation and after dosage increases, then periodically<br>• Myopathy <0.2%[l]<br>5% in combination with gemfibrozil; 2% in combination with niacin<br>• Caution in hepatic disease<br>• Caution in severe renal impairment, use lowest dose in moderate renal impairment and monitor |

[1] Adapted from PBM-MAP, 1997

[a] ac = before meals; ALT = alanine aminotransferase; ASA = aspirin; AST = aspartate aminotransferase; BAR = bile acid resin; CrCL = creatinine clearance; DM = diabetes mellitus; GI = gastrointestinal; HDL = high-density lipoprotein cholesterol; Hct = hematocrit; Hbg = hemoglobin; HMG-CoA RI = HMG CoA reductase inhibitors; IR = immediate release; LDL = low-density lipoprotein cholesterol; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; PUD = peptic ulcer disease; pwdr = powder; SR = sustained release; TC = total cholesterol; TG = triglyceride; TIA = transient ischemic attack; WBC = white blood (cell) count.

[b] McKenney, J. M. Dyslipidemias. In: Koda-Kimble, M. A., Young, L. Y., eds. Applied Therapeutics: The Clinical Use of Drugs. 6th ed. Vancouver: Applied Therapeutics Inc., 1995:9-1-9-26.

[c] Talbert, R. L. Hyperlipidemia. In: DiPiro, J. T., Talbert, R. L., Yee, G. C., Matzke, G. R., Wells, B. G., Posey, L. M., eds. (1997). Pharmacotherapy: A Pathophysiologic Approach. 3rd ed. Stamford, CT: Appleton & Lange:459-489.

[d] Antihyperlipidemic Agents. In: Hebel, S. K., ed. Drug Facts and Comparisons. St. Louis: Facts and Comparisons Inc.; 1998:171f-72p.

[e] Refer to Appendix 4 for drug interactions.

[f] At 1 year follow-up on an average dose of 4 packets/day. The Lipid Research Clinics Coronary Primary Prevention Trial. (1984). Journal of the American Medical Association.;251:351-74.

[g] Knopp, R. H., Alagona, P., Davidson, M., et al. (1998). Equivalent of a time-release form of niacin (Niaspan) given once-a-night versus plain niacin in the management of hyperlipidemia. Metabolism, 47, 1097-1104.

[h] Bennett, W. M., Aranoff, A. R., Morrison, G., et al. (1983). Drug Prescribing in Renal Failure: Dosing Guidelines for Adults. American Journal of Kidney Diseases 3(3), 155-187.

[i] Frick, M. H., Elo, M. O., Haapa, K., et al. (1987). Helsinki Heart Study. New England Journal of Medicine. 317, 1237-1245.

[j] Adkins, J. C., Faulds, D. (1997). Micronised fenofibrate. Drugs. 54, 615-633.

[k] Depending on specific agent and dose, refer to product package inserts.

[l] Bradford, R. H., Shear, C. L., Chremos, A. N., et al. (1994). EXCEL Study Results: Two year efficacy and safety follow-up. American Journal of Cardiology. 74, 667-673.

# VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DYSLIPIDEMIA** IN PRIMARY CARE

## APPENDIX 5

# Appendix 5
**Percent LDL-C Reductions to Meet Goal LDL-C**

| | Goal LDL-Cholesterol | | |
|---|---|---|---|
| Baseline LDL-C (mg/dl) | < 2 Risk Factors 160mg/dL | ≥ 2 Risk Factors 130mg/dL | Secondary Prevention 120mg/dL |
| 240 | 33% | 46% | 50% |
| 235 | 32% | 45% | 49% |
| 230 | 30% | 43% | 48% |
| 225 | 29% | 42% | 47% |
| 220 | 27% | 41% | 45% |
| 215 | 26% | 40% | 44% |
| 210 | 24% | 38% | 43% |
| 205 | 22% | 37% | 41% |
| 200 | 20% | 35% | 40% |
| 195 | 18% | 33% | 38% |
| 190 | 16% | 32% | 37% |
| 185 | xxx | 30% | 35% |
| 180 | xxx | 28% | 33% |
| 175 | xxx | 26% | 31% |
| 170 | xxx | 24% | 29% |
| 165 | xxx | 21% | 27% |
| 160 | xxx | 19% | 25% |
| 155 | xxx | xxx | 23% |
| 150 | xxx | xxx | 20% |
| 145 | xxx | xxx | 17% |
| 140 | xxx | xxx | 14% |
| 135 | xxx | xxx | 11% |
| 130 | xxx | xxx | 8% |
| 125 | xxx | xxx | xxx |
| 120 | xxx | xxx | xxx |
| 115 | xxx | xxx | xxx |
| 110 | xxx | xxx | xxx |
| For recommendation of drug that may be used to reach goal, refer to Appendix 6. | | | |

Adapted from the DoD Pharmacoeconomic Center (PEC) publication, July, 1999.

# VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DYSLIPIDEMIA** IN PRIMARY CARE

## APPENDIX 6

# Appendix 6
# Drug Selection Based on Required LCL-C Reduction[1]

| % LDL-C Reduction Required | HMG-CoA Reductase Inhibitor | | | | | |
|---|---|---|---|---|---|---|
| | Pravastatin | Fluvastatin | Ceruvistatin | Lovastatin | Simvastatin | Atorvastatin |
| 18 | 10 mg | 20 mg | 0.2 mg | 10 mg | 5 mg | 10 mg |
| 19 | | | | | | |
| 20 | | | | | | |
| 21 | 20 mg | | | | | |
| 22 | | | | | | |
| 23 | | 40 mg | | 20 mg | | |
| 24 | | | | | 10 mg | |
| 25 | | | | | | |
| 26 | | | | | | |
| 27 | | 80 mg | | | | |
| 28 | 40 mg | | 0.3 mg | 40 mg | | |
| 29 | | | | | | |
| 30 | | | 0.4 mg | | | |
| 31 | XXX | | | | 20 mg | |
| 32 | XXX | | | | | |
| 33 | XXX | | | 80 mg | | |
| 34 | XXX | | | | | |
| 35 | XXX | XXX | XXX | | | |
| 36 | XXX | XXX | XXX | | 40 mg | 20 mg |
| 37 | XXX | XXX | XXX | | | |
| 38 | XXX | XXX | XXX | | | |
| 39 | XXX | XXX | XXX | | | |
| 40 | XXX | XXX | XXX | XXX | | |
| 41 | XXX | XXX | XXX | XXX | 80 mg | |
| 42 | XXX | XXX | XXX | XXX | | |
| 43 | XXX | XXX | XXX | XXX | | |
| 44 | XXX | XXX | XXX | XXX | | 40 mg |
| 45 | XXX | XXX | XXX | XXX | | |
| 46 | XXX | XXX | XXX | XXX | | |
| 47 | XXX | XXX | XXX | XXX | XXX | |
| 48 | XXX | XXX | XXX | XXX | XXX | |
| 49 | XXX | XXX | XXX | XXX | XXX | |
| 50 | XXX | XXX | XXX | XXX | XXX | |
| 51 | XXX | XXX | XXX | XXX | XXX | |
| 52 | XXX | XXX | XXX | XXX | XXX | 80 mg |
| 53 | XXX | XXX | XXX | XXX | XXX | |
| 54 | XXX | XXX | XXX | XXX | XXX | |
| 55 | XXX | XXX | XXX | XXX | XXX | |
| 56 | XXX | XXX | XXX | XXX | XXX | |
| 57 | XXX | XXX | XXX | XXX | XXX | |

[1] Adapted from the DoD Pharmacoeconomic Center (PEC) Publication, July, 1999.

| | | | | | |
|---|---|---|---|---|---|
| 58 | XXX | XXX | XXX | XXX | XXX |

## LDL-C Reduction-Point Estimates

The point estimates provided were derived from the information obtained from the product package insert and published randomized studies. To establish an efficacy (versus effectiveness) estimate of LDL-C reduction for each drug and strength, studies and/or Product Package Inserts (PPI) must have net the following criteria: 1) published in a peer reviewed journal (not applicable to PPI) or provided in the FDA approved PPI, 2) subjects must have been randomized to treatment, 3) number of study subjects receiving each dosage strength clearly stated, and 4) duration of therapy and timing of LDL-C measurement provided. To estimate efficacy, LDL-C reductions must have been obtained at baseline and again between six and twenty-four weeks of initiation of "statin" therapy. The final point estimate for each drug and strength is a weighted average based upon the number of study subjects evaluated in each study.

References included in the determination of LCL-C reductions associated with each of the commercially available HMG-CoA RIs:

1 Arca, M., et al. (1994). Hypercholesterolemia in postmenopausal women. Journal of the American Medical Association. 271, 453-459.
2 Arnadottir, M., et al. (1994). Low dose simvastatin is a well tolerated and efficacious cholesterol lowering agent in cyclosporin treated kidney transplant recipients: double blind, randomized, placebo controlled study in 40 patients. Nephron. 68, 57-62.
3 Bakker-Arkema, R., et al. (1996). Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin , in patients with hypertriglyceridemia. Journal of the American Medical Association. 275, 128-133.
4 Bard, J. M., et al. (1995). Comparison of the effect of fluvastatin, an hydroxymethyl glutaryl coenzyme A reductase inhibitor, and cholestyramine, a bile acid sequestrant, on lipoprotein particles defined by apolipoprotein composition. Metabolism. 44, 1447-1454.
5 Bertolini, S., et al. (1997). Efficacy and safety of atorvastatin versus pravastatin in patients with hypercholesterolemia. Atherosclerosis. 130, 191-197.
6 Betteridge, D. J., et al. (1994). Comparison of lipid lowering effects of low dose fluvastatin and conventional dose gemfibrozil in patients with primary hypercholesterolemia. American Journal of Medicine. 96(Suppl 6A):45S-54S.
7 Bevilacqua, M., et al. (1997). Effect of fluvastatin on lipids and fibrinolysis in coronary artery disease. American Journal of Cardiology. 79, 84-87.
8 Blankenhorn, D. H, et al. (1993). Coronary angiographic changes with lovastatin therapy. Annals of Internal Medicine. 119, 969-976.
9 Bradford, R. H., et al. (1991). Expamded clinical evaluation of lovastatin (EXCEL) study results: Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. Archives of Internal Medicine. 151, 43-49.
10 Brown, A., et al. (1998). Treating patients with documented atherosclerosis to national cholesterol education program recommended low density lipoprotein cholesterol goals with atorvastatin, fluvastatin, lovastatin, and simvastatin. Journal of the American College of Cardiology. 32, 1-9.
11 Broyles, F. E., et al. (1995). Effect of fluvastatin on intermediate density lipoprotein (remnants) and other lipoptorein levels in hypercholesterolemia. American Journal of Cardiology. 76, 129A-135A.

12 Capurso, A., et al. (1992). Lipid control with low dose simvastatin in patients with moderate hypercholesterolemia. An italian multicentre double-blind placebo controlled study. European Heart Journal. 13(Supp B):11-16.
13 Chan, P., et al. (1995). The effectiveness and safety of low dose pravastatin in elderly hypertensive hypercholesterolemic subjects on antihypertensive therapy. American Journal of Hypertension. 8, 1099-1104.
14 Crepaldi, G., et al. (1991). Pravastatin vs gemfibrozil in the treatment of primary hypercholesterolemia. Archives of Internal Medicine. 151, 147-152.
15 Dallongeville, J., et al. (1994). Fluvastatin reduces levels of plasma Apo B-containing particles and increases those of LpA-I. American Journal of Medicine. 4, 96(suppl 6A:32S-36S).
16 Dart, A., et al. (1997). Multicenter, double-blind, one year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia. American Journal of Cardiology. 80, 39-44.
17 Davidson, M., et al. (1997). Comparison of one-year efficacy and safety of atorvastatin versus lovastatin in primary hypercholesterolemia. American Journal of Cardiology. 79, 1475-1481.
18 Davidson, M. H., et al. (1997). A comparison of estrogen replacement, pravastatin, and combined treatment for the management of hypercholesterolemia in postmenopausal women. Archives of Internal Medicine. 157, 1186-1192.
19 Davidson, M. H., et al. (1994). Fluvastatin: long term extension trial (FLUENT): Summary of efficacy and safety. American Journal of Medicine. 96, (suppl):41S-44S.
20 Davidson, M. H., et al. (1997). The efficacy and six-week tolerability of simvastatin 80 and 160mg/day. American Journal of Cardiology. 79, 38-42.
21 Davignon, J., et al. (1994). Comparative efficacy and safety of pravastatin, nicotinic acid, and the two combined in patients with hypercholesterolemia. American Journal of Cardiology. 73, 339-345.
22 Denke, M. A., et al. (1995). Effacacy of low-dose cholesterol-lowering drug therapy in men with moderate hypercholesterolemia. Archives of Internal Medicine. 155, 393-399.
23 Douste-Blazy, P., et al. Comparative study of the effacacy and tolerability of simvastatin and pravastatin in patients with primary hypercholesterolemia. Drug Investigation.
24 Farmer, J. A., et al. (1992). Comparative effects of simvastatin and lovastatin in patients with hypercholesterolemia. Clinical Therapeutics. 14, 708-717.
25 Farnier, M., et al. (1998). Cerivastatin in the treatment of mixed hyperlipidemia: the RIGHT study. American Journal of Cardiology. 82, 47J-51J.
26 Farnier, M., et al. (1994). Comparative efficacy and safety of micronized fenofibrate and simvastatin in patients with primary type Iia or Iib hyperlipidemia. Archives of Internal Medicine.154, 441-449.
27 Glasser, S. P., et al. (1996). The efficacy and safety of pravastatin in patients aged 60 to 85 years with low-density lipoprotein cholesterol > 160mg/dl/. American Journal of Cardiology. 77, 83-85.
28 Greten, H., et al. (1994). Treatment of primary hypercholesterolemia: flavastatin versus bezafibrate. American Journal of Medicine. 96, (suppl):55S-63S.
29 Heinonen, T. M., et al. (1996). The lipid lowering effect of atorvastatin, a new HMG-CoA reductase inhibitor: results of a randomized, double-masked study. Clinical Therapeutics. 18, 853-863.

30 Herd, J. A., et al. (1997). Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations. Lipoprotein and Coronary Atherosclerosis Study. American Journal of Cardiology. 80, 278-286.
31 Hunninghake, D. B. (1998). Clinical efficacy of cerivastatin:phase IIa dose-ranging and dose-scheduling studies. American Journal of Cardiology. 82, 26J-31J.
32 Illingworth, D. R., et al. (1992). Comparative hypolipidemic effects of lovastatin and simvastatin in patients with heterozygous familial hypercholesterolemia. Atherosclerosis. 96, 53-54.
33 Insull, W., et al. (1994). Efficacy and safety of once-daily vs twice daily dosing with fluvastatin, a synthetic reductase inhibitor, in primary hypercholesterolemia. Archives of Internal Medicine. 154, 2449-2455.
34 Jacobson T. A., et al. (1995). Efficacy and safety of pravastatin in african americans with primary hypercholesterolemia. Archives of Internal Medicine. 155, 1900-1906.
35 Jacobson, T. A., et al. (1994). Fluvastatin and niacin in hypercholesterolemia: a preliminary report on gender differences in efficacy. American Journal of Cardiology. 96(suppl):64S-68S.
36 Jacotot, B., et al. (1995). Comparison of fluvastatin versus pravastatin treatment of primary hypercholesterolemia. French fluvastatin study group. American Journal of Cardiology. 76, 54A-56A.
37 John, S., et al. (1998). Increased bioavailability of nitric oxide after lipidlowering therapy in hypercholesterolemic patients. A randomized, placebo-controlled, double-blind study. Circulation. 98, 211-216.
38 Jones, P., et al. (1998). Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (The Curves Study). American Journal of Cardiology. 81, 582-587.
39 Jones, P. H., et al. (1991). Once-daily pravastatin in patients with primary hypercholesterolemi: a dose-response study. Clinical Cardiology. 14, 146-151.
40 Jukema, J. W., et al. (1995). Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels:The Regression Growth Evaluation Statin Study (REGRESS). Circulation. 91, 2528-2540.
41 Keech, A., et al. (1994). Three year follow-up of the oxford cholesterol study: assessment of the efficacy and safety of simvastatin in preparation for a large mortality study. European Heart Journal. 15, 255-269.
42 Knopp, R. H., et al. (1994). Efficacy and safety of fluvastatin in patients with non-insulin dependent diabetes mellitus and hyperlipidemia. American Journal of Medicine. 96, (Suppl 6A):69S-78S.
43 Lambrecht, L. J., et al. (1993). Efficacy and tolerability of simvastatin 20mg vs pravastatin 20mg in patients with primary hypercholesterolemia. ACTA Cardiologies. XLVIX, 541-554.
44 LaRosa, J. C., et al. (1994). Cholesterol lowering in the elderly;results of the cholesterol reduction in seniors program(CRISP) pilot study. Archives of Internal Medicine.154, 529-539.
45 Lincott, C. J., et al. (1993). Treating hypercholesterlemia with HMG CoA reductase inhibitors: a direct comparison of simvastatin and pravastatin. Australian New Zealand Journal of Medicine. 23, 381-386.

46 Mc Kenney, J. M., et al. (1998). A randomized trial of the effects of atorvastatin and niacin in patients with combined hyperlipidemia or isolated hypertryglyceridemia. American Journal of Medicine. 104, 137-143.
47 McPherson, R., et al. (1992). Comparison of the short term efficacy and tolerability of lovastatin and pravastatin in the management of primary hypercholesterolemia. Clinical Therapeutics. 14, 276-291.
48 Miserez, A. R., et al. (1994). Prediction of the therapeutic response to simvastatin by pretreatment lipid concentrations in 2082 subjects. European Journal of Clinical Pharmacology. 46, 107-14.
49 Nawrocki, J., et al. (1995). Reduction of LDL cholesterol by 25% to 60% in patients with primary hypercholesterolemia by atorvastatin, a new HMG CoA reductase inhibitor. Arteriosclerotic Thrombolytic Vascular Biology. 5, 678-682.
50 Ooi, T. C., et al. (1997). Efficacy and safety of a new hydroxymethylglutaryl-coenzyme A reductase inhibitor, atorvastatin, in patients with combined hyperlipidemia: comparison with fenofibrate. Arteriosclerotic Thrombolytic Vascular Biology. 17, 1793-1799.
51 Pasternak, R. C., et al. (1996). Effect of combination therapy with lipid reducing drugs in patients with coronary heart disease and "normal" cholesterol levels. Annals of Internal Medicine. 125, 529-540.
52 Pietro, D. A., et al. (1989). Effects of simvastatin and probucol in hypercholesterolemia (Simvastatin Multicentre Study Group II). American Journal of Cardiology. 63, 682-686.
53 Pitt, B., et al. (1995). Pravastatin limitations of atherosclerosis in coronary arteries (PLAC I): Reduction in atherosclerosis progression and clinical events. Journal of the American College of Cardiology. 26, 1133-1139.
54 Product Package Insert. Atorvastatin.
55 Product Package Insert. Cerivastatin.
56 Product Package Insert. Fluvastatin.
57 Product Package Insert. Lovastatin.
58 Product Package Insert. Pravastatin.
59 Product Package Insert. Simvastatin.
60 Richter, W. O., et al. (1991). Comparative effects of two HMG-CoA reductase inhibitors (lovastatin and pravastatin) on serum lipids and lipoproteins. International Journal of Tissue Reactivity. 13, 107-110.
61 Rubinstein, A., et al. (1991). Cholesterol-lowering effects of a 10mg daily dose of lovastatin in patients with initial total cholesterol levels 200mg to 240mg/dl. American Journal of Cardiology. 68, 1123-1126.
62 Salonen, R., et al. (1995). Kuopio atherosclerosis prevention study (KAPS): a population based primary prevention trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. Circulation. 92, 1758-1764.
63 Sasaki, J., et al. (1998). A long-term comparative trial of cerivastatin sodium, a new HMG Co-A reductase inhibitor, in patients with primary hypercholesterolemia. Clinical Therapeutics. 20, 539-548.
64 Scandinavian Simvastatin Survival Group. (1994). Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the scandanavian simvastatin survival study (4S). Lancet. 344, 1383-1389.

65 Schrott, H. G., et al. (1995). Enhanced low-density lipoprotein cholesterol reduction and cost-efectiveness by low-dose colestipol plus lovastain combination therapy. American Journal of Cardiology. 75, 34-39.
66 Serruys, P. W., et al. (1999). A randomized placebo-controlled trial of fluvastatin for the prevention of restenosis after successful coronary balloon angioplasty: results of the fluvastatin angioplasty restenosis (FLARE) trial. European Heart Journal. 20(1) pp. 58-69.
67 Shepherd, J., et al. (1995). Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. New England Journal of Medicine. 333, 1301-7.
68 Simons, L. A., et al. (1992). Successful management of primary hypercholesterolemia with simvastatin and low-dose colestipol. Medical Journal of Australia. 157, 455-459.
69 Stalenhoef, A. F. H., et al. (1993). Treatment of primary hypercholesterolaemia. Short term efficacy and safety of increasing doses of simvastatin and pravastatin: a double blind comparative study. Journal of Internal Medicine. 234, 77-82.
70 Stein, E., et al. (1998). Efficacy and safety of 0.8mg dosage of cerivastatin, a novel HMG CoA reductase inhibitor. Journal of the American College of Cardiology. 31, 281A.
71 Stein, E. (1998). Cerivastatin in primary hyperlipidemia: a multicenter analysis of efficacy and safety. Journal of the American College of Cardiology. 82, 40J-46J.
72 Stein, E. A., et al. 1998) Efficacy and safety of simvastatin 80mg/day in hypercholesterolemic patients. The expanded dose simvastatin study group. Journal of the American College of Cardiology. 82, 311-6.
73 Steinhagen-Thiessen, E. (1994). Compararive efficacy and tolerability of 5mg and 10mg simvastatin and 10mg pravastatin in moderate primary hypercholesterolemia. Cardology. 85, 244-254.
74 The European Study Group. (1992). Efficacy and tolerability of simvastatin and pravastatin in patients with primary hypercolesterolemia (Multicountry comparative study). Journal of the American College of Cardiology. 70, 1281-1286.
75 The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. (1998). Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. New England Journal of Medicine.339, 1349-1357.
76 The Lovastatin Pravastatin Study Group. (1993). A multicenter comparative trial of lovastatin and pravastatin in the treatment of hypercholesterolemia. Journal of the American College of Cardiology. 71, 810-815.
77 The Pravastatin Multinational Study Group for Cardiac Risk Patients. (1993). Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. Journal of the American College of Cardiology. 72, 1031-1037.
78 The Simvastatin Pravastatin Study Group. (1993). Comparison of the efficacy, safety, and tolerability of simvastatin and pravastatin for hypercholesterolemia. Journal of the American College of Cardiology. 71, 1408-1414.
79 Wierzbicki, A. S., et al. (1998). High-dose atorvastatin therapy in severe heterozygous familial hypercholesterolemia. Quality Journal of Medicine. 91, 291-294.
80 Wiklund, O., et al. (1993). Pravastatin and gemfibrozil alone and in combination for the treatment of hypercholesterolemia. American Journal of Medicine. 94, 13-20.

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## APPENDIX 7

# Appendix 7
# Costs for Dyslipidemia Drug Therapy

| DRUG | USUAL DOSE [2] | DoD COST/MONTH [3] | VHA COST/MONTH [4] |
|---|---|---|---|
| **Bile Acid Resins** | | | |
| Cholestyramine Powder | 4 gm bid | $23.40 | $ 23.50 |
| Colestipol [5-6] | | | |
| Granules | 5 gm bid | $18.60 | $ 18.60 |
| Tablets | 4 gm bid | $18.00 | $ 18.00 |
| **HMG CoA Reductase Inhibitors** | | | |
| Lovastatin | 10-80 mg qd | $ 12.60 - $140.00 | $ 9.00 - $ 18.00 |
| Simvastatin [6] | 5-80 mg qd | $ 30.51 - $ 51.70 | $ 13.50 - $ 32.10 |
| Atorvastatin | 10-40 mg qd | 24.30 - $75.00 | $ 34.74 - $ 64.80 |
| Cerivastatin 6 | 0.2-0.4 mg qd | $ 9.00 all doses | $ 16.83 all doses |
| Fluvastatin | 20-40 mg qd | $ 13.50 all doses | $ 21.71all doses |
| Pravastatin | 10-40 mg qd | $ 20.10 - $39.00 | $ 30.97 - $ 55.99 |
| **Niacin Immediate Release** [7] | | | |
| Niacor ® | 500mg tid | $0.70 | $ 19.67 |
| **Niacin Sustained Release** | | | |
| Niaspan ® | 1.5 g (2x750 mg) qd | $20.53 | $20.53 |
| **Fibrates** | | | |
| Fenofibrate | 201 mg qd | $ 36.90 | $ 36.88 |
| Gemfibrozil | 600 mg bid | $ 2.76 | $ 4.00 |

[1] Usual doses; does not reflect equivalent doses

[2] DoD Distribution And Pricing Agreement (DAPA) Pricing 5/99; updated prices may be obtained from the Defense Supply Center Philadelphia (DSCP) on a monthly basis at 215-737-7013

[3] VHA Federal Supply Schedule (FSS) Pricing 6/99; updated prices may be obtained from the Pharmacy Benefits Management (PBM) Bulletin Board at 708-531-7947

[4] VHA National Formulary Item

[5] DoD Basic Core Formulary Item; all BCF items are available through the DoD National Mail Order Pharmacy (NMOP)

[6] Food and Drug Administration (FDA) approved niacin products

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## BIBLIOGRAPHY

**MANAGEMENT OF DYSLIPIDEMIA IN PRIMARY CARE**

## Bibliography

4S. See Scandinavian Simvastatin Survival Study Group

ACC/AHA/ACP-ASIM Guidelines. See Gibbons

AFCAPS/TexCAPS. See Downs

American College of Physicians (ACP). (1996). Guidelines for using serum cholesterol, high-density lipoprotein cholesterol, and triglyceride levels as screening tests for preventing coronary heart disease in adults. Part 1. Annals of Internal Medicine. 124(5), 515-517.

American College of Sports Medicine (ACSM) Guidelines for Exercise Testing and Prescription, Fifth Edition (1995). Baltimore: Williams & Wilkins, pp. 162, 174.

American College of Sports Medicine Position Stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness and flexibility in health adults. (1998). Medical Science and Sports Exercise. 30(6), 975-991.

American Diabetes Association (ADA). Position statement: Management of dyslipidemia in adults with diabetes. (1998). Diabetes Care. 21(1), 179-182.

Anderssen, S. A., Haaland, A., Hjermen, I., Urdal, P., Gjesdal, K., & Holme, I. (1995). Oslo diet and exercise study: a one year randomized intervention trial. Effect on haemostatic variables and other coronary risk factors. Nutrition Metabolism in Cardiovascular Disease. 5, 189-200.

Atkings, D. A. & DiGuiseppi, C. Screening for high blood cholesterol and other lipid abnormalities. In: DiGuiseppi, C., Atkins, D., Woolf, S. H., Kamerow, D. B. eds. U.S. Preventive Services Task Force. (1996). Guide to Clinical Preventive Services. Second edition. Alexandria: International Medical Publishing, 15-38.

Barrett-Connor, E., Khaw, K. (1984). Family history of heart attack as an independent predictor of death due to cardiovascular disease. Circulation. 69, 1065-1069.

Beresford, S. A., Curry, S. J., Kristal, A. R., Lazovich, D., Feng, Z., & Wagner, E. H. (1997). A dietary intervention in primary care practice: the Eating Patterns Study. American Journal of Public Health. 87(4), 610-616.

Bergstrand, R., Vedin, A., Wilhelmsson, C., Wallin, J., Wedel, H., Wilhelmsen, L. (1978). Myocardial infarction among men below age 40. British Heart Journal. 40, 783-788.

Berlin, J. A., & Colditz, G. A. (1990). A meta-analysis of physical activity in the prevention of coronary heart disease. American Journal of Epidemiology. 132, 612-628.

Blair, S. N. (1994). Physical activity, fitness, and coronary heart disease. In Bouchard, C., Shephard, R. J., Stephens, T. (eds). (1994). Physical activity, Fitness and Health: International Proceedings and Consensus Statement. Champaign, IL: Human Kinetics, 579-380.

Blankenhorn, D. H., Nessim, S. A., Johnson, R. L., Sanmarco, M. E., Azen, S. P., & Cahsin-Hemphill, L. (1987). Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. Journal of The American Medical Association. 257(23), 3233-3240.

Brown, G., Albers, J., Fisher, L., Schaefer, S., Lin, J., Kaplan, C., Zhao, X., Bisson, B., Fitzpatrick, V., & Dodge, H. (1990). Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. New England Journal of Medicine. 323(19), 1289-1298.

Brown, M. (1999). Do vitamin E and fish oil protect against ischaemic heart disease? Lancet 354(9177), 441-442.

Califf, R., Armstrong, P., Carver, J., D'Agostino, R., & Strauss, W. (1996). 27th Bethesda Conference: Matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 5. Stratification of patients into high, medium and low risk subgroups for purposes of risk factor management. Journal of the American College of Cardiology. 27, 1007-1012.

Canner, P. L., Berge, K. G., Wenger, N. K., Stamler, J., Friedman, L., Prineas, R. J., & Friedewald, W. (1986). Fifteen year mortality in coronary drug project patients: long term benefit with niacin. Journal of the American College of Cardiology. 8(6), 1245-1255.

CARE. See Sacks

Castelli, W. P. (1984). Epidemiology of coronary heart disease: the Framingham Study. American Journal of Medicine. 76(2A), 4-12.

Castelli, W. P., Garrison, R. J., Wilson, P. W. F., Abbott, R. D., Kalousdian, S., & Kannel, W. B. (1986). Incidence of coronary heart disease and lipoprotein cholesterol levels: the Framingham Study. Journal of the American Medical Association. 256, 2835-2838.

Centers for Disease Control and Prevention, National Center for Health Statistics, Division of Health Examination statistics. Unpublished data.

CLAS. See Blankenhorn

Cooper, G. R., Myers, G. L., Smith, S. J., & Schlant, R. C. (1992). Blood lipid measurements. Variations and practical utility. Journal of the American Medical Association. 267(12), 1652-1660.

Coronary Drug Project. See Guyton

Cress, M. E., Buchner, D. M., Questad, K. A., Esselman, P. C., deLateur, B. J., & Schwartz, R. S. (1999). Exercise: effects on physical functional performance in independent older adults. Journal of Gerontology Series A, Biological Sciences and Medical Sciences. 54(5), M242-8.

Criqui, M. H. & Golomb, B. A. (1998). Epidemiologic aspects of lipid abnormalities. American Journal of Medicine. 105(1A), 48S-57S.

Diabetes Control and Complications Trial Research Group (DCCT). (1995). Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. American Journal of Cardiology, 75(14), 894-903.

Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet. 354(9177), 447-455.

Downs, J. R., Clearfield, M., Weis, S., Whitney, E., Shapiro, D. R., Beere, P. A., Lagendorfer, A., Stein, E. A., Kruyer, W., Gotto, A. M., Jr. (1998). Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Journal of the American Medical Association. 279(20), 1615-1622.

Ebrahim, S. & Davey, & Smith, G. (1999). Multiple risk factor interventions for primary prevention of coronary heart disease. The Cochrane Database of Systematic Reviews. Issue 4.

Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. (1998). Archives of Internal Medicine. 158(17), 1855-1867.

Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on the detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). (2001). Journal of the American Medical Association. 285(19), 2486-2497.

FATS. See Brown G

Fiore, M. C., Smith, S. S., Jorenby, D. E., & Baker, T. B. (1994). The effectiveness of the nicotine patch for smoking cessation: a meta-analysis. Journal of the American Medical Association. 271, 1940-1947.

FLARE. See Serruys

Fletcher, G. F. (1997). How to implement physical activity in primary and secondary prevention. a statement for healthcare professionals from the task force on risk reduction, American Heart Association. Circulation 96. 355-357.

Fletcher, G. F., Balady, G., Blair, S. N., Blumenthal, J., Caspersen, C., Chaitman, B., Epstein, S., Sivarajan, Froelicher, E. S., Froelicher, V. F., Pina, I. L., & Pollock, M. L. (1996). Statement on exercise: benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. Circulation. 94(4), 857-862.

Frick, M., Elo, O., Happa, K., Heinonen, O. P., Heinsalmi, P., Helo, P., Huttunen, J. K., Kaitaniemi, P., Koskinen, P., & Manninen, V. (1987). Helsinki Heart Study: primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. New England Journal of Medicine.317(20), 1237-1245.

Friedewald, W. T., Levy, R. I., & Fredrickson, D. S. (1972). Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clinical Chemistry. 18(6), 499-502.

Frolich, J., Fodor, G., McPherson, R., Genest, J., & Langner, N. (1998). Ratinale for and outline of the recommendations of the Working Group on Hypercholesterolemia and Other Dyslipidemias: Interim report. Canadian Journal of Cardiology. 14(Suppl A), 17A-21A.

Frost, P. H. & Havel, R. J. (1998). Rationale for use of non-high-density lipoprotein cholesterol rather than low-density lipoprotein cholesterol as a tool for lipoprotein cholesterol screening and assessment of risk and therapy. American Journal of Cardiology. 81(4A), 26B-31B.

Garber, A. M., Browner, W. S., & Hulley, S. B. (1996). Cholesterol screening in asymptomatic adults, revisited. Annals of Internal Medicine. 124, 518-531.

Gibbons, R., Chatterjee, K., Daley, J., Douglas, J., Fihn, S., Gardin, J., Grunwald, M., Levy, D., Lytle, B., O'Rourke, R., Schafer, W., Williams, S., Ritchie, J., Cheitlin, M., Eagle, K., Gardner, T., Garson, A., Russell, R., Ryan, T., & Smith, S.(1999). ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Chronic Stable Angina). Journal of the American College of Cardiology. 33(7), 2092-2197.

Glover, M. U., Kuber, M. T., Warren, S. E., & Vieweg, W. V. (1982). Myocardial infarction before age 36: risk factor and arteriographic analysis. American Journal of Cardiology. 49, 1600-1603.

Glynn, T. J. & Manley, M. W. (1990). How to help your patients stop smoking: a National Cancer Institute manual for physicians. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute. NIH Publication No. 90-3064.

Gordon, D. J., Probstfeld, J. L., & Garrison, R. J. (1989). High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. Circulation. 79, 8-15.

Guyton, J. (1998). Effect of niacin on atherosclerotic cardiovascular disease. American Journal of Cardiology. 82(12A), 18-23.

Haffner, S. M., Lehto, S., Rönnemaa, T., Pyörälä, K. & Laasko, M. (1998). Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. New England Journal of Medicine. 339, 229-234.

Hall, J. A., Roter, D. L. & Katz, N. R. (1988). Meta-analysis of correlates of provider behavior in medical encounters. Medical Care. 26, 657-675.

Haskell, W. (1984). Exercise-induced changes in plasma lipids and lipoproteins. Preventive Medicine 13, 23-36.

Helsinki Heart Study. See Frick

Hjermann, I., Holme, I., & Leren, P. (1986). Oslo study diet and antismoking trial. American Journal of Medicine. 80(suppl 2A), 7-11.

Hjermann, I., Holme, I., Velve Byre, K., & Leren, P. (1981). Effect of diet and smoking on the incidence of coronary heart disease. Report from the Oslo Study Group of a randomized trial in healthy men. Lancet. ii, 1303-1310.

Holme, I., Hjermann, I., Helgeland, A., & Leren, P. (1985). The Oslo Study; diet and antismoking advice. Additional results from a 5-year primary preventive trial in middle-aged men. Preventive Medicine. 14, 279-292.

Hunt, S. C., Williams, R. R., & Barlow, G. K. (1986). A comparison of positive family history definitions for defining risk of future disease. Journal of Chronic Disease. 39, 809-821.

Joint British recommendations on prevention of coronary heart disease in clinical practice. (1998). British Cardiac Society, British Hyperlipidemia Association, British Hypertension Society. Endorsed by the British Diabetic Association. Heart. 80(2S), 1S-29S.

Jones, P. H., Farmer, J. A., Cressman, M. D., McKenney, J. M., Wright, J. T., Proctor, J. D., Berkson, D. M., Farnham, D. J., Wolfson, P. M., & Colfer, H. T. (1991). Once-daily pravastatin in patients with primary hypercholesterolemia: a dose response study. Clinical Cardiology. 14(2), 146-151.

Kannel, W. B. (1978). Hypertension, blood lipids, and cigarette smoking as co-risk factors for coronary heart disease. Annals of the New York Academy of Science. 304, 128-139.

Kannel, W. B. & McGee, D. L. (1979). Diabetes and cardiovascular disease. The Framingham study. Journal of the American Medical Association. 241, 2035-2038.

Kris-Etherton, P., Burns, J. (eds.). (1998). Cardiovascular Nutrition: Strategies and Tools for Disease Management and Prevention. The American Dietetic Association.

Leng, G. C., Price, J. F., & Jepson, R. G. (1999). Lipid-lowering pharmacotherapy for lower-limb atherosclerosis. Cochrane Database of Systematic Reviews. Issue 4.

Lipid Research Clinics Program. (1984). The Lipid Research Clinics coronary primary prevention trial results: I. Reduction in the incidence of coronary heart disease. Journal of the American Medical Association. 241, 351-364.

Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. (1998). Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. New England Journal of Medicine. 339, 1349-1357.

Lovastatin Study Groups I through IV. (1993). Lovastatin 5-year safety and efficacy study. Archives of Internal Medicine. 153, 1079-1087

MacMahon, S., Peto, R., Cutler, J., Collins, R., Sorlie, P., Neaton, J., Abbott, R., Godwin, J., Dyer, A., & Stamler, J. (1990). Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure, stroke: prospective observational studies corrected for the regression dilution bias. Lancet. 335(8692), 765-774.

Mazzeo, R. S., Cavanagh, P., Evans, W. J., Fiatarone, M., Hagberg, J., McAuley, E., & Startzell, J. (1998). American College of Sports Medicine Position Stand. Exercise and physical activity for the older adult. Medical Science and Sports Exercise. 30(6), 992-1008.

McCarron, D. A., Oparil, S., Chait, A., Haynes, R. B., Kris-Etherton, P., Stern, J. S., Resnick, L M., Clark, S., Morris, C. D., Hatton, D. C., Metz, J. A., McMahon, M., Holcomb, S., Snyder, G. W., & Pi-Sunyer, F. X. Nutritional Management of cardiovascular risk factors. A randomized clinical trial. Archives in Internal Medicine. 157(2), 169-177.

McGinnis, J. M. & Foege, W. H. (1993). Actual causes of death in the United States. Journal of the American Medical Association. 270, 2207-2212.

Medical Research Council (MRC) Working Party. (1992). Medical Research Council trial of treatment of hypertension in older adults: principal results. British Medical Journal. 304, 405-412.

Miettinen H, Lehto S, Salomaa V, Mahonen M, Niemela M, Haffner SM, Pyorala K, Tuomilento J. (1998). Impact of diabetes on mortality after the first myocardial infarction. Diabetes Care. 21(1):69-75

Multiple Risk Factor Intervention Trial (MRFIT) Research Group. Multiple risk factor intervention trial: risk factor changes and mortality results. Journal of the American Medical Association. 248,1465-1477.

National Cancer Institute (NCI). (1994). Tobacco and the clinician: interventions for medical and dental practice. NIH publication No 94-3693. National Cancer Institute, 5, 1-22.

National Cholesterol Education Program (NCEP). (1993). Second report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). NIH Publication 93-3095, National Institutes of Health, National Heart, Lung, and Blood Institute, Bethesda, Maryland.

NCEP II. Also see Summary

NCEP III. See Executive Summary

Neaton, J. D. & Wentworth, D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease: overall findings and differences by age for 316,099 white men. Archives of Internal Medicine. 152, 56-64.

NIH Consensus Conference: Triglyceride, high-density lipoprotein, and coronary heart disease. (1993). Journal of the American Medical Association. 269(4), 505-510.

Oberman, A., Kriesberg, R., & Henkin, Y. (1992). Secondary dyslipidemia. In principles and management of lipid disorders. (pp. 154-70). Baltimore: Williams & Wilkins.

Ockene, J. K. (1987). Smoking intervention: The expanding role of the physician. American Journal of Public Health. 77, 782-783.

Ockene, J. K., Kristellar, J., Goldberg, R., Amick, T. L., Pekow, P. S., Hosmer, D., Quirk, M. & Kalan, K. (1991). Increasing the efficacy of physician-delivered interventions: a randomized clinical trial. Journal of General Internal Medicine. 6, 1-8.

Oslo. See Anderssen; Hjermann; Holme

Pate, R. R., Pratt, M., Blair, S. N., Haskell, W. L., Macera, C. A., Bouchard, C., Buchner, D., Ettinger, W., Heath, G. & King, A. C. (1995). Physical activity and public health. A recommendation from the Center for Disease Control and Prevention and the American College of Sports Medicine. Journal of the American Medical Association. 273, 402-407.

Pederson, L. L. (1982). Compliance with physician advice to quit smoking: a review of the literature. Preventive Medicine. 11, 71-84.

Pharmacy Benefits Management—Medical Advisory Panel. (1999). The pharmacologic management of hyperlipidemia. VHA PBM-SHG Publication. Hines, IL: Pharmacy Benefits Management Strategic Health Group, Veterans Health Administration, Department of Veterans Affairs.

Physical activity and health: A report of the Surgeon General, U.S. Department of Health and Human Services; Center for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion. The President's Council on Physical Fitness and Sports, 1996

Piolot, A., Nadler, F., Cavallero, E., Coquard, J. L., & Jacotot, B. (1996). Prevention of recurrent acute pancreatitis in patients with severe hypertriglyceridemia: value of regular plasmapheresis. Pancreas. 13(1), 96-99.

Pollock, M. L. & Wilmore, J. H. (1990). Exercise in Health and Disease: Evaluation and Prescription for Prevention and Rehabilitation, Second Edition. Philadelphia: WB Saunders.

Post Coronary Artery Bypass Graft (CABG) Trial Investigators. (1997). The effect of aggressive lowering of LDL cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. New England Journal of Medicine 336, 152-162.

Prabhakaran, B., Dowling, E. A., Branch, J. D., Swain, D. P. & Leutholtz, B. C. (1999). Effect of 14 weeks of resistance training on lipid profile and body fat percentage in premenopausal women. British Journal of Sports Medicine. 33(3), 190-195.

Rivers JT, White HD, Cross DB, Williams BF, Norris RM. Reinfarction after thrombolytic therapy for acute myocardial infarction followed by conservative management: incidence and effect of smoking. Journal of the American College of Cardiology. 16, 340-348.

Rosenberg, L., Kaufman, D. W., Helmrich, S. P., & Shapiro, S. (1985). The risk of myocardial infarction after quitting smoking in men under 55 years of age. New England Journal of Medicine. 313, 1511-1514.

Rosenberg, L., Miller, D. R., Kaufman, D. W., Helmrich, S. P., Van de Carr, S., Stolley, P. D. & Shapiro, S. (1983). Myocardial infarction in women under 50 years of age. Journal of the American Medical Association;250(20), 2801-2806.

Rosenberg, L., Palmer, J. R. & Shapiro, S. (1990). Decline in the risk of myocardial infarction among women who stop smoking. New England Journal of Medicine. 322, 213-217.

Rubins, H. B., Robins, S. J., Collins, D., Fye, C. L., Anderson, J. W., Elam, M. B., Faas, F. H., Linares, I., Schaefer, E. J., Schectman, G., Wilt, T. J. & Wittes, J. (1999). Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of HDL-C. Veterans Affairs High-density Lipoprotein Cholesterol Intervention Trial Study Group. New England Journal of Medicine. 341(6), 410-418.

Russell, M. A. H., Wilson, C., Taylor, C. & Baker, C. D. (1979). Effect of general practitioners' advice against smoking. British Medical Journal. 2, 231-235.

Sacks, F. M., Pfeffer, M. A., Moye, L. A., Rouleau, J. L., Rutherford, J. D., Cole, T. G., Brown, L., Warnica, F. W., Arnold, J. M., Davis, B. R. & Braunwald, E. (1996). Cholesterol and Recurrent Events Trial Investigators (CARE). The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. New England Journal of Medicine. 335(14), 1001-1009.

Scandinavian Simvastatin Survival Study Group. (1994). Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). Lancet. 344, 1383-1389.

Serruys, P, Foley, D., Jackson, G., Bonnier, H., Macaya, C., Vrolix, M., Branzi, A., Shepherd, J., Suryapranata, H., de Feyter, P., Melkert, R., van Es, G. & Pfister, P. (1999). A randomized placebo-controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty; final results of the fluvastatin angiographic restenosis (FLARE) trial. European Heart Journal. 20(1), 58-69.

Shaffer, J. & Wexler, L. (1996). Reducing low-density lipoprotein cholesterol levels in an ambulatory care system. Results of a multidisciplinary collaborative practice lipid clinic compared with traditional physician-based care. Archives of Internal Medicine. 156(13), 1476-1479.

Shenberger, D. M., Helgren, R. J., Peters, J. R., Quiter, E., Johnston, E. A., & Hunninghake, D.B. (1992). Intense dietary counseling lowers LDL cholesterol in the recruitment phase of a clinical trial of men who had coronary artery bypass grafts. Journal of the American Dietetic Association 4, 441-445.

SHEP Cooperative Research Group. (1991). Prevention of stroke by antihypertensive drug treatment in older patients with isolated systolic hypertension. Journal of the American Medical Association. 265, 3255-3264.

Shepherd, J., Cobbe, S. M., Ford, I., Isles, C. G., Lorimer, A. R., MacFarlane, P. W., McKillop, J. H. & Packard, C. J. (1995). Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group (WOSCPS). New England Journal of Medicine. 333(20), 1301-1307.

Sikand, G., Kashyap, M. L., & Yang, I. (1989). Medical nutrition therapy lowers serum cholesterol and saves medication costs in men with hypercholesterolemia. Journal of the American Dietetic Association. 98(8), 889-898.

Snowden, C. B., McNamara, P. M., Garrison, R. J., Feinleib, M., Kannel, W. B., & Epstein, F. H. (1982). Predicting coronary heart disease in siblings—a multivariate assessment. American Journal of Epidemiology.115(2), 217-222.

Spate-Douglas, T. & Keyser, P. E. (1999). Exercise intensity: its effect on the high-density lipoprotein profile. Archives of Physical Medicine Rehabilitation. 80(6), 691-695.

Stamler, J. (1988). Risk factor modification trials: implications for the elderly. European Heart Journal. 9(suppl D), 9-53.

Stamler, J., Vaccaro, O., Neaton, J. D. & Wentworth, D. (1993). Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the multiple risk factor intervention trial. Diabetes Care. 16(2), 434-444.

Stein, R. A., Michielli, D. W., Glantz, J. D., Sardy, H., Cohen, A., Goldberg, N. & Brown, C. D. (1990). Effects of different exercise training intensities on lipoprotein cholesterol fractions in healthy middle-aged men. American Heart Journal. 119(2 Pt 1), 277-283.

Stone, N. J. (1997). Management of Lipids in Clinical Practice. Professional Communications, Inc. ISBN 1-884735-22-3.

Summary of the second report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. Journal of the American Medical Association. 269, 3015-3022.

Thompson, S. G., Pocock, S. J. (1990). The variability of serum cholesterol measurements: implications for screening and monitoring. Journal of Clinical Epidemiology. 43, 783-789.

Ulbright, T. L. V. & Soughgate, D. A. T. (1991). Coronary heart disease: seven dietary factors. Lancet. 338, 985-992.

United Kingdom Prospective Diabetes Study Group (UKPDS). (1998). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 353, 837-853.

U.S. Department of Agriculture, U.S. Department of Health and Human Services: Nutrition and Your Health: Dietary Guidelines for Americans. Fourth Edition. Hyattsville, MD, USDA's Human Nutrition Information Service, 1992.

U.S. Department of Health and Human Services. (1989). Reducing the health consequences of smoking: 25 years of progress. A report of the Surgeon General. DHHS Publication No. (PHS) (CDC) 8489-8411.

U.S. Preventive Services Task Force. (1996). Guide to Clinical Preventive Services. Second Edition. Alexandria, Virginia: International Medical Publishing.

VA-HIT. (1967)Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressure averaging 115 through 129 mmHg. Journal of the American Medical Association. 202, 1028-1034

Wei, M., Macera, C.A., Hornung, C.A., Blair, S.N. (1997). Changes in lipids associated with change in regular exercise in free-living men. Journal of Clinical Epidemiology. 50(10), 1137-1142.

West of Scotland Coronary Prevention Study. (1999). The effects of pravastatin on hospital admission in hypercholesterolemic middle-aged men. Journal of the American College of Cardiology. 33(4), 909-915.

Wilson, P.W., Abbott, R.D., Castelli, W.P. (1988). High density lipoprotein cholesterol and mortality: the Framingham Heart Study. Arteriosclerosis. 8, 737-741.

Wilson, P.W., D'Agostino, R.B., Levy, D., Belanger, A.M., Silbershatz, H., Kannel, W.B. (1998). Prediction of coronary heart disease using risk factor categories. Circulation. 97(18):1837-1847.

Wingard, D.L., Barrett-Connor, E., Criqui, M.H., Suarez, L. (1983). Clustering of heart disease risk factors in diabetic compared to nondiabetic adults. American Journal of Epidemiology. 117(1),19-26.

Wood, D.A., De Backer, G., Faergeman, O., Graham, I., Mancia, G., Pyorala, K. (1998). Prevention of coronary heart disease in clinical practice. Summary of recommendations of the Second Joint Task Force of the European Society of Cardiology and other societies on coronary prevention. Atherosclerosis.140(2), 199-270.

Wood, P.D., Haskell, W.L., Blair, S.N., William, P.T., Krauss, R.M., Lindgren, F.T., Albers, J.J., Ho, P.H., Farquhar, J.W. (1983). Increased exercise level and plasma lipoprotein concentrations: A one-year randomized, controlled study of sedentary middle-aged men. Metabolism. 32, 31-39

Zimmerman, F.H., Cameron, A., Fisher, L.D., Grace, N. (1995). Myocardial infarction in young adults: angiographic characterization, risk factors and prognosis (Coronary Artery Surgery Study Registry). Journal American College Cardiology. 26, 654-661.

# VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **DYSLIPIDEMIA** IN PRIMARY CARE

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